The Journal of
CLINICAL ENDOCRINOLOGY

VOLUME 2 MARCH, 1942 NUMBER 3

An Association of Short Stature, Retarded Sexual Development and High Urinary Gonadotropin Titers in Women[1]

[Ovarian Dwarfism]

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IT HAS BEEN a common and reasonable presumption that the association of unusual shortness of stature and retarded genital development bespeaks hypopituitarism, especially in the absence of cretinism, gross malnutrition or systemic disease. Even when roentgenological examination of the skull and studies of the visual fields are normal this presumption persists, fortified by a wealth of physiological data establishing the hypophysis as a controlling agent both for growth and for gonadal function and by our knowledge that demonstrable destructive pituitary disease produces similar physical consequences. Low titers of urinary gonadotropins would be expected in such people. However four short girls with deficient sexual development excreted 200 to 500 mouse units of gonadotropins per day, as judged by induced estrin production in the immature mouse, values corresponding to those of the castrate and usually taken to suggest primary ovarian insufficiency. Coincidentally, Albright, Smith and Fraser (1) have had an identical experience at the Massachusetts General Hospital as has Rakoff (2) in Philadelphia. Shelton (3) noted, such findings several years ago, but the methods of study then available did not warrant publication in his opinion in view of the paradoxical character of the results. Our own data are given here with the expectation that several gaps in our knowledge of this circumstance will be filled by the accumulated work of the other groups.

METHODS

Twenty-four-hour samples of urine or multiples thereof were used. In *patients A.B., R.F.*, and *V.F.*, all urine was collected in the hospital by voiding directly into bottles kept in the refrigerator. In the others collections were made at home during cool weather, the urine being kept as cool as possible and placed in the refrigerator as soon as it was received at the hospital. The urine was not allowed to stand

Received for publication December 1, 1941.
Read before the twenty-fifth annual meeting of the Association for the Study of Internal Secretions at Atlantic City, New Jersey, May 3, 1941.
[1] This work was supported in part by grants from the Otho S. A. Sprague Memorial Foundation and from Armour and Company.

more than five days in the refrigerator (3° C.) before the concentration was begun. No change in activity occurs within this time.

The PH of the urine was adjusted to 4.8 to 5.2 with glacial acetic acid, four volumes of 95 per cent ethanol were added with shaking, and the mixture allowed to stand in the freezer (−3° C.) for 18 to 24 hours.

The supernatant fluid was siphoned off and the suspended material remaining transferred to a cylinder, allowed to settle, decanted, and the precipitate collected after centrifugation. The precipitate was washed once each with 95 per cent alcohol, absolute alcohol, and ether, the residual ether being removed by reduced pressure. This dry powder is stable and can be stored until assay.

Preliminary to assay the crude alcohol precipitate was extracted three times with 25 cc. of water for each 24 hours of collection represented by the urine sample. These aqueous extracts, the last of which should be nearly colorless, were combined and dialyzed overnight in viscose tubes against running tap water. The dialyzed extracts were then precipitated by the addition of four volumes of acetone in the presence of a small amount of sodium acetate. The precipitate was collected by centrifugation and dissolved in water for assay. A stock solution was made, aliquots of which were taken and further diluted as necessary. Each animal, regardless of the dose of active material, received the same volume of solution.

This procedure constitutes a modification of that of Heller and Heller (4) who introduced the practice of dialysis. The assay is modified from Levin and Tyndale (5).

The assay was performed on immature female mice weighing 6 to 8 grams. Injections were made twice daily for three days. On the fifth day the animals were killed and the uterus, free from connective tissue and any intrauterine fluid, was weighed on a sensitive Roller-Smith torsion balance. The mouse unit adopted is a uterine weight twice that of controls examined in parallel.

No attempt is made to fit given uterine responses to a predetermined curve. Injection was made at three levels of dosage using four mice per level and reassay was performed if necessary to secure an observed range from negative to positive response. The levels most often used are designed to test for the following:

Normal	10, 20, 30, 40, 50 M. U. per day
Intermediate	60, 75, 100, 125 M.U. per day
High	150, 200, 250, 300, 350, 400, 450, 500 M.U. per day.

It is not contended that such a method gives complete recovery of gonadotropic material. Two of us will show elsewhere that losses of not more than 25 per cent occur, particularly during dialysis. The findings reported here, however, deal with variations in the neighborhood of 400 per cent or more.

The assays for androgens and estrogens in the urines of *patient A.B.* and *R.F.* were performed by Beach and Coffman by techniques previously described (6, 7).

DISCUSSION

By the assay method just described and in terms of the mouse unit given above, normal women thus far examined excrete from less than 10 to as high as 50 M.U. per day in the urine and postmenopausal women from 100 to 550 M.U. per day. Since methods of preparing and assaying urinary gonadotropins differ so widely, comparison of these figures with those of others must be tentative. Our data do not, however, depart widely from those of workers using tannic acid as a precipitant according to Levin's technique (8) and assaying by the uterine weight method of Levin and Tyndale (5) on immature mice. Roughly speaking, normal women excrete from less than 5 to as high as 50 M.U. per day by these procedures, the higher values occurring in one or more peaks during the cycle (8–12). Postmenopausal women excrete 100 to 400 M.U. per day (11). The same general relationships are apparent in the recent studies of Heller and Heller (13), using alcohol as a precipitant and the rat uterine response as a biological endpoint, and indeed in less quantitative fashion in earlier work which cannot be reviewed here.

There is in general little modern systematic study of urinary gonadotropins in children. Such as there is indicates low titers until adolescence and then higher values for some little time before menarche (14). Neither here nor in the earlier semiquantitative approximations is there evidence of any physiological increase in urinary gonadotropins to castrate levels before or during normal puberty. Unfortunately no data are available concerning the transient amenorrheas so frequently interposed into the early years of menstrual life.

The high titers of urinary gonadotropins of 200 to 500 M.U. per day recorded here in short girls (table 1) are thus well beyond any comparable normal value of ours or others and above anything known to occur in normal childhood or adolescence. These girls presented several features in common. They varied from 4 ft., 6 in. (138 cm.) to 4 ft., 10½ in. (149 cm.) in height. Two of them, *R.F.* (age 26) and *A.B.* (age 19), are apparently no longer growing; one, *B.W.* (age 16), has not grown in the past year and will probably grow very little more judging from the state of her epiphyses; the tallest, *P.X.* (age 17), has grown 5 cm. in the past three years and may well

grow further. The heights of these girls correspond closely to those in the series of Albright, Smith and Fraser (1) in which heights of 4 ft., 6 in. to 4 ft., 8 in. appear with regularity. No distinctive skeletal disproportion occurs. The sitting height index

$$\left(\frac{\text{sitting height} \times 100}{\text{standing height}}\right)$$

of *B.W.* of 54.9 is somewhat above the average of 53.5 derived from Shuttleworth's data for girls of 17 menstruating after 14.5 years, indicating relatively short legs. That for *P.X.* is 48.5, indicating relatively long legs. *A.B.* with an index of 52.7 corresponds closely to the average. Osseous development including epiphyseal fusion is much less retarded than in Ecke's series (15) of theatrical midgets ranging from 105 to 129 cm. in height. The hands lag 2 to 10 years behind Todd's standard (16) (table 2). Elsewhere there is less delay, in part because of the standards used; those given by Hodges (17) from the literature, are considerably more liberal than Todd's roentgenological samples, based upon rigidly selected healthy children. In the knee of *B.W.* fusion seems even in advance of Hodges' standards, and that of the ankle in accordance with it. Osteoporosis is quite distinct in three individuals (*A.B.*, *R.F.*, *B.W.*).

In three subjects spontaneous menstruation has not occurred; in one (*B.W.*) three or four periods occurred

TABLE 1. URINARY GONADOTROPINS IN GIRLS AND WOMEN WITH RETARDED SEXUAL DEVELOPMENT

Subject and age	Height, ft.-in.	Menses	Breasts	Pubic hair	Collection period, days	Urinary gonadotropins,[1] M.U./day
R.F., 26	4-7½	0[2]	0[2]	Sparse[2]	2	350
					2	300–350
					2	250–300
A.B., 19	4-9½	0	0	Sparse	3	250
					3	400–450
B.W., 16	4-6	3–4x	+	Sparse	3	250–350
P.X., 16	4-10½	0	+	Sparse	2	200–250
					2	400–500
E.S., 18	4-10	0	0 (Fat)	Sparse	3	<10
V.D., 22	6-0	0	0	+	2	<10
V.F., 20	4-8	0	0	Masculine	3	<10

[1] By mouse uterine growth assay method.
[2] Intermittent vaginal bleeding, development of breasts and pubic hair under influence of stilbestrol.

in the year and a half between the age of 14½ and 16 but none within the subsequent year. Breast development was never apparent spontaneously up to the ages of 26 in *R.F.* and 19 in *A.B.*, was slight but progressing in *B.W.* between 16 and 17 and is now beginning in *P.X.* at 17. Physical evidences of estrogen production by the ovaries of these girls may thus be absent or intermittent and delayed. Estrogens in the urine of the two studied (*A.B.*, *R.F.*) were less than the equivalent of 5 micrograms of theelin per day (50 I.U.), values approached by the normal woman usually only during or just after menstruation. Pubic and axillary hair were poorly developed in all subjects, although considerable but not excessive down could be seen elsewhere. True hirsutism was not seen. Urinary androgens in the two studied (*A.B.*, *R.F.*) were 2 to 5 I.U. per day, far below those of the normal woman, a point in agreement with the low values for 17-ketosteroids as determined colorimetrically in the series of Albright, Smith and Fraser (1) and recorded by Fraser, Forbes, Albright, Sulkowitch and Reifenstein (18).

TABLE 2. STATE OF EPIPHYSEAL FUSION[1] IN SHORT WOMEN WITH HIGH URINARY GONADOTROPIN TITERS

	Subject and Age				Normal age of fusion,[2] yr.
	R.F., 24 yr.	A.B., 19 yr.	B.W., 16 yr.	P.X. 17 yr.	
Hand					
Distal phal.	cl	cl–o	cl	cl	
Med. phal. II–V	o	o	o	o	
Prox. phal. I	o	cl–o	o–cl	cl–o	15–19
II–V	o	o–cl	o–cl	o–cl	
Metacarp.	o–cl	cl–o	cl–o	cl–o	
Radius	o–cl	o	o–cl	o	21–25
Ulna	cl–o	o	o–cl	o–cl	20–24
Estimated age (Todd, 15)	$13^{3/4}$–$15^{1/4}$	$13^{3/4}$	$13^{3/4}$–$14^{1/4}$	$13^{3/4}$	
Elbow					
Humerus	cl	cl	cl	cl	14–17
Med. epicondyle		cl–o			18
Shoulder					
Acromion		o		o	19–21
Head humerus		o–cl		o	20–23
Corocoid				cl–o	16–18
Ankle					
Calcaneous			cl		16
Tibia		o–cl[3]	cl–o		15–19
Fibula		o–cl[3]	cl–o		15–19
Knee					
Femur	cl–o	cl–o	cl–o	cl–o	20–23
Tibia	cl–o	cl–o	cl–o	o–cl	19–24
Fibula	cl–o	o–cl	cl–o	o–cl	22–24
Hip and Pelvis					
Major innominate masses		cl[3]		cl	14–16
Iliac crest		cl		o	20–25
Femur head and trochanters		c		cl	17–20

[1] *o* Refers to an open epiphyseal line, *cl* to closure. The gradation between the two is expressed by *o–cl* and *cl–o*.
[2] From Hodges (16).
[3] At age 18.

In neither our girls nor in any of the Boston series was gross pituitary disease demonstrable by skull roentgenograms of visual fields, nor was physiological evidence of hypopituitarism apart from short stature disclosed. All of the patients felt well and possessed

ordinary energy with the possible exception of *B.W.* Albright, Smith and Fraser (1) found no increased sensitivity to insulin in their subjects. The basal metabolic rates were normal (−7, −10, −8) save in *P.X.* (−25). No conclusive evidence of hypothyroidism was apparent, the low basal rate in *P.X.* being unaccompanied by elevation of blood cholesterol, and the response of the subject to thyroid treatment being unimpressive. While hypothyroidism can-

TABLE 3. EFFECTS OF URINARY GONADOTROPIN OF *patient R.F.* ON GENITALIA OF HYPOPHYSECTOMIZED RATS

A. Male hypophysectomized rats

Total dose	Final body wt.	Testes	Prostate	Seminal vesicles	Changes in gonad
M.U.	gm.	mg.	mg.	mg.	
0	65	65	2.8	4.0	
20	55	134	3.0	4.0	Tubular growth
40	61	166	2.0	4.0	Slight int. cell
80	67	670[1]	8.8	12.7	stimulation with highest dose

B. Female hypophysectomized rats

	Ovaries	Uterus	Vagina, patency	
	mg.	mg.		
0	52	11.6	19.7	cl	
20	65	35.0	80.5	cl	Diffuse follicular
40	65	49.5	106.9	cl	growth; thecal hypertrophy; 2 corpora lutea with highest dose

[1] Testes descended.

not be excluded as a factor in *P.X.* it is difficult to defend its decisive importance.

As far as our studies have gone the type of substance excreted in the urine of one of our short patients (*R.F.*) did not differ decisively from that in the urine of postmenopausal women, as described by Levin and Tyndale (19). Table 3 shows that the effect of a moderate dose was to produce diffuse enlargement of the ovarian follicles of the hypophysectomized rat, together with some thecal hypertrophy, and to increase estrin secretion. A high dose (40 M.U.) produced luteinization of an occasional follicle only. The testicular tubules of the hypophysectomized male rate were enlarged by all doses and androgen production was increased only by the highest dose (80 M.U.). Since some question now exists as to whether follicular growth in response to pituitary extracts is necessarily associated with enhanced estrogen secretion, we have avoided the term FSH (follicle-stimulating hormone) in our discussion despite the prominence of follicular growth in these experiments. All assays recorded are based upon induced estrogen secretion only and designations are best confined to the end point used.

CASE HISTORIES

Patient R. F., age 26 (referred by Dr. I. Becker). The patient, of Bohemian extraction, was said to have weighed 4½ lb. at birth, and was calculated by a midwife to have been two weeks premature. She remained smaller than her contemporaries throughout her growth period which terminated, it is believed, between the ages of 14 and 16. Spontaneous breast development and menstruation have never occurred. Save for troublesome headaches which are apparently migrainous, she has been well. She has always done well in school.

The family history suggests inheritance of slow genital development. Her mother's breasts are stated to have been immature until 20, at which time menarche occurred. The mother's mother did not menstruate until 20 but subsequently had twelve children. The patient's mother is 5 ft., 3 in. tall, her father was 6 ft. tall, and save for one grandmother who was said to have been somewhat under 5 ft. in height there is no indication of the occurrence of distinctly short individuals in the stock.

The patient was a short, pudgy, fairly well proportioned woman, 141 cm. (4 ft., 7 in.) tall, weighing 44.7 kg. (98 lb.).

The mammary areas which may or may not have been composed largely of fat were only slightly elevated and bore small poorly developedni pples. Axillary and pubic hair were sparse. There was a moderate amount of terminal hair in the burnside area and some down on the upper lip, all well within normal limits. The vulva was well formed but immature. The vagina was 2 to 3 cm. long with thin atrophic mucosa; the cervix and corpus uteri were tiny. Subsequent attempts to secure endometrial biopsies yielded no tissue. The adnexae could not be felt. The clitoris was slightly more prominent than expected from the infantile character of the rest of the genital area.

Roentgenograms showed a small shallow sella turcica with complete bony bridging of the clinoid processes and no evidence of erosion. Visual fields on two occasions in June 1939 showed tubular vision. Examination at 2 meters showed no augmentation of the visual field over that recorded at 1 meter, indicating a functional derangement. Three subsequent examinations showed varying constriction less extreme than at first and neglible in the last instance. No other evidence of hysteria has appeared. The fundi were normal and neurological examination was negative.

Roentgenograms of the long bones showed considerable osteoporosis. The data on epiphyseal closure are given in table 2. The initial basal metabolic rate was −7 (Mayo Foundation standard as given by Boothby, Berkson, and Dunn, 20). Routine examination findings of the blood and urine, including the Wassermann and Kahn reactions, were normal.

From June 13, 1939, to April 5, 1940, she received varying amounts of stilbestrol orally, chiefly 1 mg. daily, with frequent interruptions due to nausea. During this time there was considerable growth of the breasts with deep pigmentation of the nipples, increase in pubic hair, and recurrent uterine bleeding. Davis (21) has described this response in his account of the effects of stilbestrol. From April 5 to Aug. 14, 1940, she received pregnant

mare's serum gonadotropin, supplemented by stilbestrol suppositories, 0.5 mg. each, one to two nightly. No influence attributable to the gonadotropic substance was obtained.

Assays for urinary androgens (capon's comb) gave the low values of 2 and 5 I.U. per day. Assays for estrogens showed less than the equivalent of 5 μg. of theelin per day. Assays for gonadotropins were performed 6 weeks after the discontinuance of stilbestrol and the results are given in table 1.

Patient A. B., (fig. 1), age 19 (referred by Dr. Sarah Janson). The patient, of American stock, was of normal size until approximately 5 or 6 years old when she began to lag behind her contemporaries in growth. At about this time she lived with a faddist aunt who restricted meat, starches, and sugar intermittently for some five years. Subsequently, her care was assumed by her stepmother who fed her well. No obvious defects were apparent in her diet when we saw her. The growth history for the last 10 or 12 years is inexact and it is not clear at what time her present height was reached. The breasts have not developed and menses have not appeared. She is intelligent and feels well. No family history of unusual growth or development was obtained.

The patient is a short slender girl with childish contours. When first seen at the age of 18 she was 145.1 cm. tall (4 ft., 9 in.) with a sitting height of 76.4 cm. and a span of 146 cm. She weighed 38 kg. (85.5 lb.). She has grown no more than 1 cm. in the course of one year of observation but has gained 5 lb. in weight. No breast tissue was palpable, there being only a suggestive localization of fat in the mammary area. The nipples were small. A scant amount of pubic hair was present and no axillary hair. Considerable down was present on the extremities and in the burnside area of the face. The labiae were infantile. A thin ribbon-like corpus uteri was felt. The adnexae were impalpable.

Roentgenograms of the sella turcica revealed a normal structure and the visual fields were unaltered. The long bones showed generalized osteoporosis. The state of the epiphyseal development is given in table 2.

The initial basal metabolic rate was −10 (Mayo Foundation Standard) and a subsequent value was −4. Routine urine and blood examinations, including the Wassermann and Kahn reactions, were normal.

Assays for urinary androgens gave the low values of 2 and 5 I.U. per day (capon's comb), those for estrogens slightly less than the equivalent of 5 μg. of theelin.

Treatment for nine months with a mixed pituitary extract availed nothing. Subsequent to the gonadotropin assays reported here (table 1) treatment with stilbestrol has yielded some breast development and intermittent uterine bleeding.

Patient B. W., (fig. 2) age 17 (referred by Dr. C. L. Dunham), The patient, of native Anglo-Saxon stock, weighed 4½ lb. at birth and has always been smaller than other children of her age, although no exact records are available. Menses occurred first at 14½ years of age, and have recurred every six months until the age of 16. None have appeared in the ensuing year. The flow lasted 1½ to 2 days, and required 2 to 3 pads per period. There was no pain. Between periods a white, odorless vaginal discharge occurs. It is believed that the breasts have increased somewhat in size since childhood. Save for a tendency to tire easily the girl has been well. Intelligence is good. The family history provided no evidence of genital abnormalities. Her mother's grandmother had been "very short," and her mother's mother and mother's sister's daughter were 6 ft. tall. There was no other evidence of unusual skeletal growth.

The patient was a thin, well-proportioned, gracile child, 138 cm. (4 ft., 6 in.) tall at 16, weighing 32.6 kg.

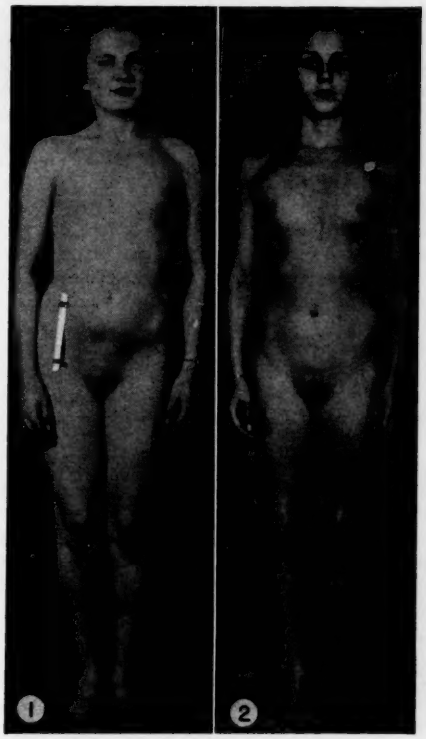

Fig. 1. *Patient A.B.* AT THE AGE OF 19. She was 4 ft. 9 in. tall and had never menstruated.

Fig. 2. *Patient B.W.* AT THE AGE OF 17. She was 4 ft. 6 in tall and had menstruated three to four times beginning at 14½ years.

(72 lb.). She did not grow between 16 and 17 years of age. Her sitting height was 75.7 cm., her span 142 cm. The mammary glands were underdeveloped but grew distinctly between examinations at 16 and 17. A tuft of axillary hair and scant pubic hair was present. Limb hair was well developed, facial hair not abnormal. The external genitalia were well formed, but immature, and the corpus uteri was small. The adnexae were impalpable.

Roentgenograms of the skull were normal. The fundi and visual fields were normal. Data on the epiphyseal development are given in table 2. The initial basal metabolic rate was −8 (Mayo Foundation Standard). The urea

clearance was 35 (UV/B, normal range, 60–90) at age 16 and 31 at age 17, and the blood urea nitrogen values were 16.2 and 11.1 mg. per cent, respectively. No explanation for the reduced renal function is known. The serum calcium was 10.5 and serum inorganic phosphorus 3.5 mg. per cent. Bone changes attributable to renal rickets were absent. No abnormalities were demonstrable in the urine; the hemoglobin, cell counts and Wassermann and Kahn reactions were normal.

The patient had had and was given no treatment. Gonadotropic assays were performed at the age of 16.

Patient P. X., age 17 (referred by Dr. H. T. Ricketts). The patient, of native Anglo-Saxon stock, was of normal size until about the age of 12 when she began lagging behind others of her age. From the age of 14, when our measurements gave a height of 144 cm. (4 ft., 8½ in.) to the present, when she is 149 cm. (4 ft., 10½ in.) tall, she has grown 5 cm. (2 in.) in height. This is about half the 4½ in. given by Richey (22) as the average growth between these ages for girls menstruating later than 13 years. In this same period she has gained from 46.3 kg. (102 lb.) to 50.8 kg. (112 lb.). She has not menstruated as yet and no evidence of breast development appeared until within the past year, although she was carefully examined several times. Breast tissue masses, 5 by 6 cm. in diameter, are now present and apparently growing. Pubic hair was very sparse until within the past year when it has thickened distinctly and axillary hair has recently appeared. She is intelligent and active, showing no sign of ill health. While several members of the subject's family are relatively short and heavy, no evidence of gross growth or genital disturbance is known in the stock.

The subject is a short, stocky, well-proportioned girl with childish contours. Her standing height is now 149 cm., her sitting height 72.2 cm., span 150.3 cm. Breast tissue and axillary and pubic hair are increasing in amounts as described above. Body and facial hair is otherwise scant. The vulva is prepubertal, the cervix small, the corpus uteri small and difficult to feel, the adnexae impalpable.

Roentgenograms of the sella turcica showed nothing unusual. Fundi and visual fields were normal. Data on epiphyseal development are given in table 2. The initial basal metabolic rate was −27 (Mayo Foundation Standard) at the age of 14, and a blood cholesterol was 168 mg. per cent. No good clinical evidence of hypothyroidism was apparent. On 1 grain of thyroid daily for three weeks the basal metabolic rate rose only to −23. Thyroid has been taken with protracted interruptions since. Early in 1939, at 15 years of age, the basal metabolic rate was −25 and −21 while she was taking ½ grain daily. In June, 1939, it was −19 after taking one grain daily for 6 weeks. Since then 1 grain has been taken daily with consistency. Two grains daily was said to have caused palpitation and was refused after a brief trial. In January, 1940, her basal rate was −12 and in November, 1940, −19 (age 16). It remains highly doubtful whether her increase in height is due in any way to thyroid substance. Her growth of 3 cm. between February, 1938, and March, 1939, when dosage was no more than ½ grain irregularly for four months of the year, was greater than the 2 cm. since then when dosage has been better sustained at a level of 1 grain daily.

Routine blood and urine analysis findings were normal.

Gonadotropic assays were performed in January and November, 1940, while she was on thyroid substance, before and during the progressive development of secondary sex characters.

All short girls with retarded sexual development do not show excess urinary gonadotropins. Thus *E.S.*, an obese girl, 4 ft., 10 in. tall, who had not as yet menstruated at the age of 18 and who had grown little pubic or axillary hair and possessed little breast tissue discernible from mammary fat, showed a low value in one assay available (table 1). No intracranial disease was demonstrable. Save for obesity and the complete closure of all epiphyseal lines of the hand, one would be tempted to group her with the others. Whether such clinical features will permit prediction of gonadotropin titers in any large series remains to be seen. Low urinary gonadotropins would certainly be expected in short individuals with proved destructive pituitary disease. The work of Albright, Smith and Fraser (1) provides ample evidence that high titers, at least, are not found among dwarfish, sexually immature people whose physiological defects are so numerous as to lead to the use of the term 'pan-hypopituitarism' in their description. Lack of vitality, low basal metabolic rate, sensitiveness to insulin, and occasionally at least a positive response to the low-salt-high-potassium regime of Cutler, Power, and Wilder (23) may distinguish these patients from those with which we are primarily concerned. Whether sharp distinctions on such metabolic grounds can always be made between those with high and low urinary gonadotropin titers must remain uncertain for the present.

Patient V.F., cited in table 1, is an example of a short woman who had never menstruated or developed breasts at the age of 20, but in whom a deep voice, well developed musculature, abundant body hair of masculine distribution, and hypertrophied clitoris attested to the active secretion of a masculinizing hormone by the ovaries or adrenals. Her small stature was due to premature fusion of the epiphyses of the long bones, giving relatively short extremities. As would be expected no excess gonadotropin was found in her urine, sufficient androgenic activity being present to reduce pituitary gonadotropin secretion. No difficulty enters into the clinical segregation of such an individual from our other subjects.

There is little information concerning urinary gonadotropins of underdeveloped women who are not short. One of our patients (*V.D.*), age 22, who was 6 ft. tall, and whose body showed eunuchoid elonga-

tion of the extremities, had infantile genitalia, flat breasts, rather sparse axillary and pubic hair and had never menstruated. She excreted less than 10 M.U. of gonadotropic material per day in her urine (table 1). One should not, however, assume that high gonadotropin titers in primary amenorrhea are restricted to short women.

A completely satisfactory interpretation of the association of shortness of stature, genital impairment and high urinary gonadotropin titers is difficult at present. The well-known increase in urinary gonadotropins in women after castration makes it entirely reasonable that ovarian insufficiency is responsible for this particular phenomenon and indicates that the anterior pituitary of our subjects can at least secrete as much gonadotropic material as that of castrate or menopausal women. To hold that that same anterior lobe is defective in its capacity to secrete growth hormone involves departure from a unitarian explanation of the syndrome. Association of an isolated defect in the growth-promoting properties of the anterior lobe with ovarian insufficiency is required. On the other hand it is difficult to explain the shortness of stature on the basis of ovarian insufficiency in view of the tallness of certain women with profound gonadal defects (e.g. *patient V.D.*). Certain pathological studies are of great interest in connection with this problem although they further illustrate difficulties rather than solve them.

Seven autopsies on short women with ovarian aplasia, often reaching the equivalent of castration, and fairly intact hypophyses may provide evidence for conditions for high urinary gonadotropin titers (24–30). The subjects ranged from 132 cm. (4 ft., 4 in.) to 148 cm. (4 ft., 10 in.) tall, averaging 139 cm. (4 ft., 6½ in.). They were fairly well proportioned and not obese. Intelligence was as a rule adequate and health was usually good until the fatal illness. Breast development was in abeyance, sexual hair sparse, and the external genitalia juvenile but well formed. None had ever menstruated. Certain epiphyseal cartilages were noted as incompletely ossified long beyond the normal age. In no instance was normal ovarian epithelium found at autopsy although several authors searched diligently for ectopic tissue. In two (29, *case 1*; 30) strands or masses of epithelium were found at ovarian sites but definitive follicular organization was not apparent. Wolffian remnants were common at the ovarian sites. Despite the ovarian aplasia, uteri, tubes, and vaginae were on the whole well formed although small. The hypophyses varied in size and were often described as rich in eosinophiles but lesions explaining the growth defects were absent. These cytological descriptions deviate often from those of increase in basophiles with prominent vacuolation noted by Biggart (31) in human castrates and by Severinghaus (32) in postmenopausal women. Difficulties in staining and enumeration of the cells may or may not account for the discrepancies. Rössle (27) was under the impression that the human castrate hypophysis was rich in eosinophiles and hence similar to that of several of these short people. The thyroid and adrenal glands were usually normal. The thymus was never hypertrophic and varied from probably normal (25) to fragmentary microscopic residua (27).

The clinical similarity of this group of patients to ours and to those of Albright, Smith and Fraser (1) is manifest and such functional findings as ours would be expected from these pathological descriptions if one waives the questionable points in pituitary cytology. Ovarian aplasia cannot, however, be regarded as invariable in short women with high gonadotropin titers. The several spontaneous menstrual periods in *patient B.W.* attest to the activity of her ovaries at times at least, and the progressive growth of breasts in *patient B.X.* indicates active ovarian secretion even while the gonadotropin titers are high.

The physical associations of ovarian aplasia are not always those of the group above. Pela's (33) subject, 36 years old, was 178.2 cm. (5 ft. 10 in.) tall at the time of death although she was said to have been short at 18. Her extremities were relatively long, her breasts flat, sexual hair sparse, and genitalia infantile. No ovarian epithelium was found at autopsy. The hypophysis was said to have been rich in eosinophiles much as in the short people. Humphreys' unpublished autopsy on a 34-year-old patient of one of us showed only minute ovaries comprised entirely of stroma. The subject was 170.1 cm. (5 ft., 6¾ in.) tall with eunuchoid skeletal proportions, flat breasts and infantile genitalia. She did, however, possess pubic and axillary hair. Assays showed estrogens in the neighborhood of 0.5 to 0.7 μg. of theeline equivalents per liter of urine, very low values, and androgens (capon's comb) to be 15 I.U. per liter. The hypophysis was not grossly altered nor were any adenomata found. The cell types are as yet incompletely studied. Unfortunately, we were not prepared to examine for urinary gonadotropins at this time. Pich's (29) 29-year old woman (*case 3*) with mammary hypoplasia, absence of sexual hair, and infantile genitalia with partial failure of fusion of the uterine anlagen had primordial follicles in her ovaries. The hypophysis showed a slight hypertrophy of chromophobe elements. She was 156 cm. (5 ft., 1 in.) tall.

Rössle (34) advanced the concept of 'sexogenous dwarfism' in 1923 on the basis of the autopsy later reported with Wallart (27), and held the ovary to be essential for normal growth. He accounted for the tall hypogonad woman on the assumption that minimal

amounts of ovarian secretion sufficient to stimulate growth but insufficient to develop the breasts and enlarge the uteri are secreted. The ovarian aplasia in Pela's (33) tall woman seems as profound, however, as in any of the dwarfish women described.

It is probable from the recent report of Thompson (35) on the effects of estradiol benzoate in underdeveloped girls that the estrogens do stimulate growth in height and, if the phenomena of normal puberty are any guide (36), the threshold for such stimulation

TABLE 4. URINARY GONADOTROPINS IN MEN AND BOYS WITH RETARDED SEXUAL DEVELOPMENT

Subject and age	Height, ft.-in.	Collection period, days	Urinary gonadotropins, M.U./day	Remarks
R.D., 12	4·4	3	10–20	Dwarfism; bilateral non-descent of testes; some pubertal growth of prostate
F.S., 16	4·10½	3	10	Retardation 2nd sex characters
R.S., 16	5·3	3	60–75	Retardation 2nd sex characters
17	5·7	1	75–100	Good progress, 2nd sex characters
M.S., 19	6·0	3	50–60	Retardation 2nd sex characters
J.K., 26	6·0	3	<10	Eunuchoid
N.D., 33	5·9	4	<10	Eunuchoid
D.V., 34	5·11	1	20	Eunuchoid

may be reasonably low. Unpublished studies of our group demonstrate that estradiol benzoate will induce nitrogen retention although the effectiveness of physiological amounts of the normal ovarian secretions in this regard is not known. We are not disposed accordingly to dismiss the importance of estrogens in the growth phenomena of normal puberty, poorly defined as this rôle is. While it is quite conceivable that in some individuals with poor growth endowment an absence of an adolescent spurt might make for some eventual shortening of stature, the existence of tall women with such profound ovarian defect as Pela describes makes it unlikely that ovarian insufficiency alone necessarily induces permanent gross shortness. Other influences beside any emanating from the gonads probably operate during adolescence and share in determining the eventual height of the individual. Such influences indeed must be present in the male to explain both the now well-defined effects of testosterone on somatic growth of undergrown boys (37–41) and the admittedly normal height eventually reaches by those with permanent testicular insufficiency. A critical serial study of epiphyseal plates in short women at favorable ages is highly desirable as the behavior of these cartilages under whatever influence may be of considerable importance. Thus in *patient B.W.* the state of epiphyseal cartilages in the lower extremities does not encourage expectation of further elongation of the legs. In Pela's subject on the other hand or in our *patient V.D.*, in both of whom a substantial delayed growth was recorded, retardation in ossification of important cartilaginous plates must have occurred. Such indeed was well demonstrated in *V.D.* at the age of 22.

There is also some question as to whether ovarian insufficiency accounts for the low androgen values in the urine of *patients A.B.* and *R.F.* and the low 17-ketosteroids found by Fraser et al (18). Castration of the adult woman cannot as yet be said to reduce the urinary steroid titers. The adrenal cortex, presumably an important source of feminine androgens, may accordingly be involved primarily or secondarily in the syndrome conceivably with important metabolic consequences.

The conclusion must be that no unified endocrine explanation of the association of shortness of stature, impaired ovarian function, and high gonadotropin titers is as yet satisfactory. The association of growth and ovarian defects may be of genetic rather than of physiologic significance and the growth-promoting pituitary functions may or may not be involved. Despite the considerable similarity of several of these people it is by no means clear that the cause is always the same. It is conceivable that dietary restrictions during childhood, as in *patient A.B.*, or obscure illness may have played an injurious rôle in some. Whatever the interpretation may be it seems likely that this group is a relatively important one among undergrown, sexually immature women and the complexity of defects forbids the casual application of the term hypopituitarism to these people.

A word of caution must be interposed against assuming that high gonadotropin titers necessarily mean permanently crippled ovaries. Such appears to be the case in some instances (*R.F.*, age 26), but in both *P.X.* and *B.W.* some progress in breast growth is occurring at age 17 and it may be that a satisfactory menstrual life will make a delayed appearance in them. Indeed such high gonadotropin titers may not be rare in those with delayed menarche and may represent an extraordinary pituitary effort required to impel genital maturation.

It is of interest that we have not as yet observed indisputably high gonadotropin titers in the few sexually underdeveloped boys and men thus far examined (table 4) although the experience of Fraser and his coworkers (18) indicates that such occasionally occurs in eunuchoids. The closest to this is shown in the case of *patient R.S.* who underwent a delayed normal pubescence at a time when his urinary

gonadotropins were at least higher than most normal individuals show.

SUMMARY AND CONCLUSIONS

By alcohol precipitation and assay by the mouse uterine weight method gonadotropins excreted in normal and castrate or menopausal urine may be measured by their capacity to increase estrin production by the immature mouse ovary.

Normal women excrete from less than 10 to as high as 50 M.U. per day, menopausal women from 100 to 550 M.U. per day.

Four short girls, 4 ft., 6 in. to 4 ft., 10½ in. tall, with retarded sexual development, excreted 200 to 500 M.U. per day, values equal to those of the castrate and usually taken to suggest primary ovarian insufficiency.

Moderate doses of the material in the urine of one subject were shown to stimulate the diffuse growth of ovarian follicles and of seminiferous tubules of hypophysectomized rats.

These girls were not obese, were fairly well proportioned, showed little breast development and little sexual hair. As far as is known, the accessory genitalia were well formed though hypoplastic, and menses occurred infrequently if at all. Retardation in completion of epiphyseal fusion at the wrists was often present in comparison with Todd's standard but was not regularly distinct there or elsewhere by more liberal standards. Basal metabolic rates were usually normal. Urinary androgens and estrogens were low in the two cases studied. No evidence of gross pituitary lesion was adduced on clinical study.

The relationship of this group to a series of autopsies describing ovarian aplasia is discussed.

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Effect of Single Injections of Estradiol Benzoate on the Normal Human Menstrual Cycle with Special Reference to the Problem of Estrogen Sensitivity

[Ovarian Response to Estrogen]

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DESPITE THE FACT THAT estrogens are extensively used in clinical gynecology, from the literature available it appears that, with one exception (1), there is no information concerning the effect of estrogens on the human ovary. Even when estrogen has been used to postpone the onset of menstruation in normal women (2) it has not been possible to predicate how it was accomplished except that it is commonly stated that this hormone inhibits temporarily the gonadotropic function of the anterior lobe of the pituitary.

The understanding of the action of estrogen in the human female is further complicated by the fact that even in laboratory mammals and especially in primates there is still a paucity of data as to how estrogen affects the normal ovary.

According to Allen, Hisaw and Gardner (3) estrogens given over long periods of time inhibit the ovary. The ovaries of mice after treatment with 500 I.U. of estrogen weekly for 150 days are usually small (3). Allen (4) found that estrogen administered to immature monkeys for 23 days caused a decrease in weight of the ovaries and some atresia of the Graafian follicle. Ball and Hartman (5) using the palpation method of Hartman (6) have shown that repeated administration of estrogen in the first part of the cycle significantly delayed ovulation in the Macacus rhesus.

The effects of single injections of estrogen in rabbits and rats apparently have not been consistent. In 40 to 50-gm. rats Hohlweg (7) claims to have induced corpus luteum formation by the administration of a single large dose of estrogen. Desclin (8) confirmed this observation but Bachman (9) failed to duplicate Hohlweg's results. In rabbits, moreover, Bachman was unable to recognize any change in the minute anatomy of the ovaries 48 hours after a single injection of a large amount of estrogen.

In the baboon, however, the single administration of adequate amounts of estradiol benzoate in the first part of the cycle leads to the rapid development of massive atresia of all of the follicles and only after 10 to 16 days have intervened does the ovary recover sufficiently to continue its normal rhythms (10, 11).

These observations in the baboon were materially assisted by the fact that this animal has a remarkable sexual skin restricted to the perineal region. During the normal menstrual cycle the perineum varies greatly in its size depending upon whether the baboon is in the first or in the second half of the cycle. By measuring daily the maximum width of this swelling it is now possible to follow the day to day progress of the menstrual cycle. The slightest deviation from normal ovarian activity is promptly reflected in alteration in the size of this perineal swelling.

Since there is no external indicator to reflect the day to day progress of the human menstrual cycle other techniques have to be employed for this purpose. The vaginal smear method and endometrial scrapings have been extensively used, but even these methods have not proved consistently reliable, as the available information is still inadequate to allow any interpretation of the factors which may produce deviations from the normal, nor can we say with any degree of certainty in these abnormal cases what is happening to the ovary.

The length of the menstrual cycle must necessarily reflect ovarian activity, but the data so far accumulated only allow of a partial interpretation of aberrations in the length of the human cycle. For this reason it is still necessary to use animal experiments in order to obtain some idea of the ovarian dysfunc-

Received for publication January 28, 1942.

tion in relation to the altered menstrual rhythm.

The animals used for this purpose must be those which respond in a manner similar to the human female.

Thus far, one such animal is the baboon and in the first correlational study (12) it was demonstrated that there is a marked similarity in the way the baboon and the human female react to progesterone. The only salient difference was one of dosage. Since the altered rhythms induced in baboons with progesterone are, generally speaking the same as in women, it follows that any recognizable change in the ovaries of baboons during such experiments most probably find their counterpart in the human ovaries under similar experimental conditions.

The present study is the second of such correlational studies between the human female and the baboon but in this instance estradiol benzoate was used instead of progesterone. The results of the investigation in baboons have already appeared (10, 11). Detailed reference will be made to these findings in the body of this paper, but in general it was shown that single injections of adequate amounts of estradiol benzoate in the first part of the cycle produce measurable changes in the size of the perineum and in the length of the menstrual cycle. From this study it was possible to obtain quantitative data on the amounts of estrogen necessary to produce disturbances in the menstrual rhythm.

In the present study it is my main purpose to show that single injections of estradiol benzoate given to women in the first part of the cycle can also cause disturbances in the menstrual rhythm. By utilizing the data obtained from baboons an attempt will be made to explain the nature of the menstrual disturbances induced in women. At the same time attention will be drawn to the existence in women of different degrees of sensitivity to estrogen and the technique will be briefly discussed as to how this sensitivity may be recognized clinically.

These results, moreover, will be reviewed in order to discover whether they are of any practical value in assessing spontaneous aberrations of the menstrual cycle in women. Finally it is also the purpose of this paper to show the need for elaborating some technique for assisting in prognosticating the tendency towards disease in so-called normal women.

MATERIAL AND METHODS

The women who subjected themselves to these experiments were unmarried. More than three quarters were under 30 and the remainder were between 30 and 40 years of age. With 4 exceptions each woman had recorded her cycles on a calendar for at least 6 months preceding the experiments. In each instance intramuscular injections of estradiol benzoate[1] were given on the 8th day of the cycle, counting the onset of menstruation as *day one*.

Each woman formed the subject of a single experiment except one, who was first injected with 1 mg. of estradiol benzoate (*case 7*) and was again treated subsequently with 5 mg. of estradiol benzoate (*case 6*).

EXPERIMENTAL RESULTS

Effect of 5 mg. of estradiol (*cases 1–6*). On examining table 1 it is evident that 5 mg. of estradiol benzoate produced three sets of results. First, in *case 1* and 3, the cycle was shortened and bleeding was precipitated 11 days after the injection in *case 1* and after 9 days in *case 3*. Second, the length of the cycle was almost doubled in *cases 2* and *4* and third in *cases 5* and *6* the cycle was slightly lengthened.

It follows therefore that in every case the menstrual rhythm was significantly disturbed by 5 mg. of estradiol benzoate.

Effect of 1 mg. of estradiol benzoate (*cases 7–11*). Again three types of responses were elicited with 1 mg. of estradiol benzoate, two of which were similar to those seen after giving 5 mg. of estradiol. Two women (*cases 8, 9*) bled prematurely on the 17th and 19th day of the cycle, i.e., 9 and 11 days respectively after receiving the injection. One woman (*case 9*) bled again on the 31st day, i.e., she experienced two periods of four days each in the same month and therefore intracyclic bleeding was induced with estradiol in the same way as occurred in some women after progesterone (12) and as Zondek and Rozin (13) reported in all of their experimental cases. In two women the cycle was lengthened (*cases 10, 11*) but only by 3 days in one instance (*case 11*). The lengthening in this latter instance could scarcely be regarded as significant. The third type of response (*case 7*) was negative, i.e., the length of the cycle was unaffected. It was this person who was later injected again but this time with 5 mg. of estradiol. Her response to this high dosage was already mentioned (*case 6*).

With one exception (*case 7*), and possibly two (*case 11*) the menstrual cycle was definitely disturbed by 1 mg. of estradiol. When the cycle was lengthened it was in no instance as great as that obtained in some women (*cases 2, 4*) after 5 mg. of estradiol. For this reason it was found expedient to use a smaller dose of estradiol in the next series of experiments.

Effect of 0.1 mg. of estradiol benzoate (*cases 12–16*). With this lowered amount of estradiol not a single woman bled prematurely. In two instances definitely (*cases 12, 14*) and possibly in a third (*case 13*) the cycle was lengthened by a few days, whereas

[1] The estradiol benzoate (Progynon b. oleosum) used was supplied by Schering Corporation.

in *cases 15* and *16* the length of the cycle was in no way disturbed.

Effect of 0.01 mg. of estradiol benzoate (cases 23–27). In none of these five women was there any detectable deviation in the length of the cycle from the normal. It is just possible that all of these women might have been resistant even to 1 mg. of estradiol benzoate as instanced by *case 7*. This possibility however, cannot be completely excluded especially in view of the small size of the group. On examining the results of the previous experiments however, it seems likely that 0.01 mg. of estradiol is incapable of influencing the human menstrual cycle.

TABLE 1. EFFECT ON THE HUMAN MENSTRUAL CYCLE OF SINGLE INJECTIONS OF ESTRADIOL BENZOATE GIVEN ON THE 8TH DAY OF THE CYCLE

Case No.	Amount of estradiol	Length of normal cycle	Length of experimental cycle
	mg.	*days*	*days*
1	5	29	19
2	5	25	45
3	5	29	17
4	5	28	44
5	5	25	31
6[1]	5	28	36
7[1]	1	28	28
8	1	28	17
9	1	28	19 (31)
10	1	28	35
11	1	29	32
12	0.1	22	27
13	0.1	29	31
14	0.1	28	33
15	0.1	25	25
16	0.1	27	27
17	0.5	26	31
18	0.5	25	31
19	0.5	23	29
20	0.5	28	19
21	0.5	27	16
22	0.5	26	26
23	0.01	25	25
24	0.01	27	26
25	0.01	28	28
26	0.01	32	33
27	0.01	29	28
28	sesame oil	28	27
29	sesame oil	28	28
30	sesame oil	25	24
31	sesame oil	26	27

[1] The same woman. Injected first with 1 mg. (*case 7*) and later with 5 mg. (*case 6*).

Effect of 0.5 mg. of estradiol benzoate (cases 17–22). The results of this experiment are shown in table 1, and in general are similar to those found after using 1 mg. of estradiol. Only 1 woman bled prematurely.

Effect of sesame oil alone (cases 28–31). It is well known that some women are easily upset by the slightest emotional disturbance. In order to eliminate the possibility that such a disturbance might have altered the menstrual rhythm in the numerous cases mentioned above, 4 women were injected with pure sesame oil. The cycles of these women were undisturbed. If these results are taken in conjunction with those of *cases 23* to *27*, it is clear that 9 women were in no way affected as a sequence of the pain experienced during the injection.

DISCUSSION

Disturbance of the menstrual rhythm. In a previous paper (12) it was shown that the administration of progesterone, either as a single or multiple dose, noticeably influenced the human menstrual cycle. In such instances the cycle may be significantly shortened or lengthened or again intracyclic bleeding may sometimes be induced. In this latter condition despite the premature bleeding menstruation occurs at the normally expected time and two bleedings are therefore experienced in one month.

In baboons single injections of estrogen on the 8th day of the cycle may lengthen the cycle by 10 to 15 days or by 6 to 8 days depending on the amount of estrogen used. In only 1 of 10 baboons was the cycle shortened and in this instance by as much as 12 days (10).

Generally speaking the human female responds to single injections of estradiol benzoate in a fashion similar to that described for the baboon. The length of the cycle may be almost doubled (*case 2*) or else it may be lengthened by only 3 to 8 days (*cases 11, 6*). In one woman (*case 9*) two bleedings occurred in one month, the one 11 days after treatment and the other 3 days later than the normally expected time. In this woman, therefore, intracyclic bleeding was induced in the same way as after progesterone except that after estrogen the premature bleeding took 4 days longer to appear than after progesterone. Although premature bleeding can be consistently induced intracyclic hemorrhage has so far not been produced in the baboon either with estrogen or progestogen.

With the exception of *case 9*, the cycle succeeding the experimental one was of normal length although in two instances it was shorter by 3 to 5 days than the normal.

Factors responsible for disturbing the cycle. In castrate baboons the perineal swelling is completely absorbed. Repeated treatment with estrogen causes the perineum of castrate baboons to swell to enormous dimensions, but when the estrogen is withdrawn the perineum decreases in size until it returns to its resting level. Within 10 to 16 days of the last injection of

estrogen bleeding occurs. Such bleeding is obviously of the estrogen withdrawal variety (10). The deturgescence of the perineum and the latent period of 10 to 16 days after the withdrawal of estrogen in castrate baboons are important factors in facilitating our understanding of what precisely happens when estrogen is injected into normal baboons; without understanding the reactions of normal baboons to estrogen it is impossible to comprehend the nature of the responses seen in women.

By the 8th day of the cycle the perineum of normal baboons is as a rule considerably swollen or turgescent (compare figs. 1 and 2). If to such baboons 1 to 5 mg. of estradiol benzoate is administered the perineum increases still further in size for an average of 5 days. Thereafter perineal deturgescence is initiated and it continues until the perineum returns to rest. On an average of 14 days after the injection, turgescence recurs and the perineum then passes through an almost normal rhythm of turgescence, deturgescence and rest. The menstrual cycle in such instances is prolonged by as much as 16 to 20 days.

The fact that the turgescent perineum of these normal baboons underwent deturgescence following the estrogen treatment seemed to suggest that either the production of endogenous estrogen was curtailed or else this exogenous estrogen stimulated the formation of progestogen since either the withdrawal of estrogen or the presence of progestogen can induce deturgescence (14, 15, 16). Examination of the ovaries revealed the absence of any recent corpus luteum, but massive atresia of the large and medium sized Graafian follicles was a characteristic finding (11).

It might be argued that atretic follicles were the source of progestogen and that premature deturgescence was enforced by this hormone. It has been shown, however, that progestogen can induce deturgescence which is maintained for 4 to 7 days only and since the deturgescence produced by estrogen lasted for 10 to 16 days it seems unlikely that the precocious formation of progestogen could have accounted for this prolonged deturgescence of the perineum. On the other hand the atresia of the follicles very strongly suggests that the exogenous estrogen suspended estrogen production by the ovaries by a destruction of the stratum granulosum. The cells of this part of the follicle are usually regarded as being responsible for the elaboration of estrogen. The latent period of 10 to 16 days implies the withdrawal of estrogen. Besides, in normal baboons, treated paradoxically enough with 0.1 mg. of estradiol benzoate, deturgescence was prematurely initiated and bleeding supervened 12 days after the injection, i.e., about the same time as occurs before estrogen withdrawal bleeding appears in castrates.

Why estrogen withdrawal bleeding should be precipitated in only 1 of 10 baboons is difficult to explain, but it may be that towards the end of the induced deturgescence in the 9 baboons the ovaries recovered and commenced to elaborate estrogen before the bleeding threshold had been reached. The single baboon which bled might have been sensitive, just as will be described later for women, and the ovarian inhibition was so intense that the endogenous estrogen was elaborated only after the estrogen level had fallen below the bleeding threshold.

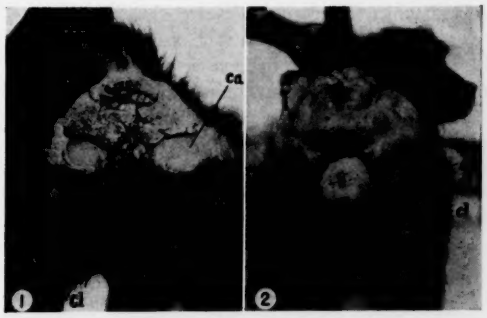

Fig. 1. PERINEAL REGION OF AN ADULT BABOON A FEW DAYS BEFORE MENSTRUATION. Note the collapsed lobe (*cl*), the exposed callosities (*ca*). This stage is known as perineal rest.

Fig. 2. PERINEAL REGION OF THE SAME BABOON A FEW DAYS BEFORE OVULATION. Note the enormous clitoral lobe (*cl*), the callosities (*ca*) are almost covered by the swollen perineum. This stage is known as perineal turgescence.

Small amounts of estradiol (0.1 mg.) cause only a partial inhibition of the turgescent perineum which may decrease in size by a few inches and thereafter it returns to its original dimensions to pass through a normal rhythm. The length of the menstrual cycle is increased by 4 to 6 days and this is equivalent to the period during which the perineum was temporarily depressed. In this latter case the injected estrogen produced only a partial inhibition of the ovaries which in turn was responsible for the incomplete perineal deturgescence (11).

In normal baboons, therefore, 1 to 5 mg. of estradiol given in the first part of the cycle causes complete perineal deturgescence lasting on an average of 14 days and thereafter the perineum goes through an almost normal rhythm but the cycle is considerably lengthened, whereas 0.1 mg. of estradiol leads to partial perineal deturgescence lasting for 4 to 6 days and the cycle is slightly lengthened but in this instance only for 4 to 6 days. Still smaller amounts of estrogen (0.5 mg. of estradiol) have a recognizable effect neither on the perineum nor on the length of the cycle.

With these facts before us it is now possible to proceed to analyze the effects of estrogen on the human cycle. Disregarding for the time being the question of susceptibility it is evident that in *cases 2* and *4* the cycle was greatly prolonged and in this respect the prolongation can be compared with the reactions of baboons treated with 1 to 5 mg. of estradiol. Naturally, in women it is not possible to watch the day to day progress of events as is possible in baboons. It was especially emphasized that the period of inhibition after estrogen administration in normal baboons is equivalent in length to the latent period which intervenes between the last injection of estrogen into castrates and the onset of withdrawal bleeding. The cycle in baboons is prolonged approximately to the same extent as the period of induced perineal inhibition. It is possible to arrive at an appraisal of the prolonged cycle in women in the same way as in baboons. To achieve this it is necessary to know in castrate women the interval that elapses between the last treatment with estrogen and the onset of withdrawal bleeding.

It is remarkable that despite the numerous occasions on which castrate women have been treated with estrogen so little attention has been devoted to this latent period. It is particularly fortunate that Elden (17) submitted detailed protocols in his experiments in which he attempted to produce a progestational reaction in the endometrium of castrate women. In the three cases reported by Elden the latent period varied from 5 to 9 days. In *cases 1, 3, 8, 9, 20, 21* (table 1) bleeding supervened in normal women between 8 days (*case 21*) and 11 days (*cases 1, 9, 20*). Combining Elden's figures with those adduced from the present study it seems that the extremes of the latent period lie between 5 and 11 days.

Using *case 4* as an example it is now possible to arrive at an assessment of how the cycle was lengthened in women after estrogen treatment.

a) Duration of the spontaneous cycle before estrogen was injected	8 days
b) Duration of inhibition by estrogen in normal women is equivalent to the length of the latent period before estrogen withdrawal bleeding supervenes	5 to 11 days
c) Total number of days of spontaneous cycle before injection of estrogen plus the duration of inhibition by exogenous estrogen	8+5 to 11 =13 to 19 days
d) Length of normal cycle	28 days
e) Length of experimental cycle	45 days
f) Difference in length between experimental and normal cycle	45−28 =17 days

It is seen that *f* falls within the limits of *c*. If *case 2* is examined in this manner it will be seen that *f* also falls within the limits of *c*.

If the above interpretation should prove to be valid it is obvious that a new cycle was initiated without the intervention of bleeding after the period of ovarian inhibition induced by the exogenous estrogen. In other words, the extent of prolongation of the experimental cycle is equivalent to the sum of the number of days the normal cycle progressed before the injection of the estrogen plus the length of time the ovaries were prevented from producing estrogen. The latter is equal to the latent period intervening before estrogen withdrawal bleeding is precipitated in castrate women.

This interpretation receives additional confirmation from the results obtained in *cases 1, 3, 8, 9, 20, 21*. Bleeding supervened in all of these cases within 8 to 11 days of the injection of the estrogen. The next bleeding occurred with two exceptions at the normally expected interval dating the first day of the new cycle as commencing on the first day of the experimentally induced bleeding. If we add the length of the experimental cycle to the normal we find that in every instance the total length of the two cycles is approximately similar to the experimental cycle of *case 2* and *4* (table 1). This is also reflected in table 2.

TABLE 2

Case No.	Length of normal cycle	Length of experimental cycle	Combined lengths of both cycles
	days	*days*	*days*
1	29	19	48
3	29	17	46
8	28	17	45
20	28	19	47
21	27	16	43

Case 9 cannot be included as she had 2 shortened cycles.

There can be no doubt that the administration of estrogen produced a profound inhibition of the ovaries and the follicular atresia was probably so extensive that from the time of the administration of the estradiol the ovaries in these women ceased producing estrogen and hence they behaved in a manner identical with that of castrate women who had received a course of estrogen and then the treatment had been suspended. The latent period intervening between the injection of estrogen and the onset of bleeding in the cases quoted above is, if anything, a little longer in some instances than the latent period given by Elden for his castrates. The correspondence is so close that this can scarcely be regarded as fortuitous.

It follows that in *cases 2* and *4* the exogenous es-

trogen was adequate to overwhelm almost completely the ovaries and that an almost new cycle was initiated. In those cases which bled prematurely the ovarian inhibition was so profound and the follicular atresia so extensive that by the time the exogenous estrogen had been metabolized the estrogen threshold had fallen so low that withdrawal bleeding occurred and only then was a new cycle initiated.

The greatly prolonged cycle and the much shortened cycle can be regarded as almost identical responses to estrogen except that in the former endogenous estrogen commences to exert its effect before the estrogen has fallen below the threshold value and so bleeding is avoided. Such women may be regarded as having a more stable endocrine balance than those who bled prematurely.

The slightly prolonged cycle experienced by *cases 5, 6, 10, 11, 12, 13, 14, 17, 18* and *19*, however, require to be considered in a slightly different way. Again this analysis is only possible by considering the behavior of baboons. It has been pointed out that in two baboons treated with 0.1 mg. of estradiol benzoate the turgescent perineum undergoes partial deturgescence lasting for 6 to 8 days and therefore the perineum swells once and goes through a normal rhythm except that the cycle is slightly lengthened. In these baboons the ovaries have only been partially inhibited.

Those women with a slightly lengthened cycle have probably reacted in the same way as the two baboons treated with 0.1 mg. of estradiol. The extent of the lengthening of the cycle is obviously related to the degree of ovarian inhibition. Those women who were resistant suffered from very slight inhibition of the ovaries and consequently the cycle was only prolonged by a few days. When the inhibition was more intense the cycle was prolonged by 8 days. The lengthening in such cases then is dependent on the resistance or sensitiveness of women to estrogen. This matter will be more fully dealt with at a later stage in this paper.

In general all types of reactions noticed in baboons can be excited in women, although premature bleeding can be produced frequently in women and rarely in baboons. Although the administration of estrogen to baboons in the first part of the cycle leads to massive follicular atresia this reaction in the ovaries still remains to be demonstrated in women. The effect of estrogen on the human and baboon cycles is so remarkably similar that it is more than likely that the follicles in the human subject also undergo atresia. The conclusive proof for the existence of this atresia in the human female must await histological confirmation.

Calibration of the estrogen production of the ovaries by means of exogenous estrogen. It is not possible as yet to state whether the follicular atresia induced by estrogen in baboons is caused indirectly by inhibiting the pituitary or whether this is due to a direct action by estrogen on the stratum granulosum. Whichever way this exogenous estrogen exerts its effects there can be no question that almost all the follicles undergo atresia.

It is known from studies of other endocrine glands that it is possible to inhibit the action of a gland by administering the specific hormone elaborated by that gland. DeRobertis (18) has demonstrated that a single administration of parathormone leads to a diminution of the volume with retraction of the cytoplasm and hyperchromasy of the nucleus of the cells of the parathyroid gland of the rat. Hydropic degeneration of the parathyroid cells may also occur and this is sometimes associated with the accumulation of colloid substance. Similarly Gersch and Grollman (19) caused the X zone in the mouse suprarenal to disappear by giving small doses of cortical hormone. These investigators are of the opinion that the X zone acts as a reserve tissue which can be depressed when the need for cortical secretion is satisfied in some other way. Gillman and Stein (20) suggested that the cystic corpus luteum which normally forms during the early months of pregnancy in women was due to the retention of secretion, because this was now being elaborated elsewhere. If we accept the thesis that a specific exogenous hormone can cause inhibition of the endocrine gland elaborating that hormone then the fact that estrogen causes the stratum granulosum of the Graafian follicle of the baboon to degenerate affords strong evidence that the stratum granulosum is responsible in part at least for the production of estrogen and conversely that degeneration of the stratum granulosum of all the large follicles is evidence that the production of estrogen by the ovaries is suspended.

Since the inhibition of estrogen formation in the baboon is associated with perineal deturgescence, it follows that if adequate amounts of exogenous estrogen cause complete perineal deturgescence, then it is reasonable to presume that such exogenous estrogen completely inhibited the production of endogenous estrogen. The induction of partial perineal deturgescence on this basis is regarded as resulting from incomplete ovarian inhibition.

In the baboon 1 to 5 mg. of estradiol benzoate caused complete perineal inhibition. For this reason it was suggested that the baboon was producing less than the equivalent of 1 to 5 mg. of estradiol benzoate. Per contra, since 0.1 mg. caused partial deturgescence in 2 baboons and complete deturgescence in a third baboon it was suggested that the ovary was producing just less than, or the equivalent of, 0.1 mg. of

estradiol benzoate, especially as in two additional baboons 0.05 mg. did not visibly effect the size of the perineum nor the length of the menstrual cycle.

By thus calibrating the exogenous estrogen against the endogenous estrogen, using the perineum as an indicator, it was possible to state that the baboon produces almost an equivalent of 0.1 mg. estradiol on the 8th day of the cycle. There is no doubt that the amount of estrogen necessary to inhibit the ovaries can be established for every adult baboon.

In the same manner the amount of estrogen required to inhibit the human ovaries can also be established. It has already been shown that estrogen administered to women in the first part of the cycle can either greatly lengthen the cycle or greatly shorten it or again it may only slightly lengthen the cycle. The first two responses have been regarded as evidence of complete ovarian inhibition, whereas the slightly lengthened cycle was regarded as a partial inhibition.

On this basis therefore it would appear that when the cycle was greatly lengthened or significantly shortened the amount of exogenous estrogen (estradiol) was more than the equivalent of endogenous estrogen, whereas when the cycle was slightly lengthened the endogenous estrogen was almost balanced by the exogenous estradiol benzoate.

From table 1 it is evident that 0.01 mg. of estradiol given on the 8th day did not significantly alter the cycle of any of the 5 women, whereas 0.1 mg. caused a lengthening of 2 days in *case 13*, and of 5 days in *cases 12* and *14*, and no effect in *cases 15* and *16*. It is doubtful whether the lengthening of the cycle in *case 13* can be regarded as significant and it is impossible to adduce any other evidence in support of or against this as is so easily possible in the baboon. We can say moreover, that in 2 of 5 women (*cases 12* to *16*) 0.1 mg. of estradiol benzoate was able to produce partial inhibition of the ovaries, i.e., 3 women were elaborating more than the equivalent of 0.1 mg. of estradiol benzoate whereas 2 women were elaborating almost the equivalent of 0.1 mg. of estradiol benzoate.

When 0.5 mg. of estradiol was injected in 2 women the cycle was significantly shortened (*cases 20, 21*), in three women the cycle was moderately lengthened (*cases 17, 18, 19*) and in one woman (*case 22*) there was no apparent effect on the length of the cycle. This indicates that in some women, the ovary was elaborating less than the equivalent of 0.5 mg. of estradiol benzoate (*cases 20, 21*), whereas in others (*cases 17, 18, 19*) it was elaborating almost the equivalent and, in *case 22*, more than the equivalent, of 0.5 mg. of estradiol benzoate. Further, after 1 mg. of estradiol the cycle of every woman was affected except that of *case 7*. This woman was later injected with 5 mg. of estradiol benzoate (*case 6*) and her cycle was increased in length by 18 days. The experiments on this woman (*case 6, 7*) illustrate very forcibly the fact that partial inhibition is reflected in a slight lengthening of the cycle. In every one of the 6 cases, the cycle was affected by 5 mg. of estradiol benzoate.

From these experiments it is abundantly evident that by using estradiol benzoate it is possible to disturb the cycle provided that sufficient amounts of the hormone are administered. It is not possible to establish the efficacy or otherwise of a particular quantity of the estradiol to inhibit the ovaries within a few days as in baboons, but that it can be done by carefully watching the length of the cycle, which takes several weeks, there can scarcely be any doubt from the results shown in table 1.

The estrogen formed by the human ovary, therefore, can be calibrated against exogenous estrogen, using the length of the cycle as an indicator. The interpretation of the findings however, involves a consideration of another factor which will be examined seriatim.

The existence of estrogen-sensitive and estrogen-resistant women. On closely perusing table 1 it is at once clear that there is a great variation in the resistance or sensitivity of different women to estrogen. Thus one woman will be resistant to as much as 1 mg. of estradiol benzoate (*case 7*) and yet in another 0.5 mg. not only affects the length of the cycle but actually precipitates premature bleeding (*case 21*). In some women the cycle may be disturbed by as little as 0.1 mg. of estradiol (*case 14*). This means that in some women the ovary can resist as much as 1 mg. of estradiol benzoate whereas in others it is sensitive to as little as 0.1 mg. *Case 7* is a good example of a resistant type, since after 1 mg. of estradiol benzoate the cycle was unaffected, and when injected later with 5 mg. of estradiol benzoate the cycle was lengthened only by 8 days. The fact that *case 5* showed a slight lengthening of the cycle indicates that she too may be regarded as a type resistant to estradiol and that she too might have been refractory to 1 mg. of estradiol. Per contra *case 9* may be regarded as a sensitive type because not only was her cycle shortened, but the succeeding cycle also was impaired as she bled 12 days after her induced bleeding. This second bleeding may be regarded as an estrogen withdrawal bleeding and it is unlikely that she ovulated during the month in which she experienced two periods. Similarly, *cases 20* and *21* may be regarded as sensitive since 0.5 mg. was able to precipitate bleeding prematurely.

On the basis of whether the cycle is shortened, greatly lengthened, slightly lengthened or unaffected after treatment with estradiol benzoate it is possible

to grade women as very sensitive, sensitive, slightly sensitive or resistant. Thus *case 7* can be regarded as an example of type resistant to estrogen, since 1 mg. of estradiol did not influence the cycle whereas 5 mg. only produced a slight lengthening of the cycle. *Case 21*, on the other hand, may safely be regarded as being a very sensitive type in that 0.5 mg. of estradiol considerably shortened the cycle, whereas *case 18* can be classed as slightly sensitive to estrogen and *case 14* may be classified as being sensitive or even very sensitive.

The existence of types sensitive to hormones other than estrogen is being steadily established. Himsworth (21) mentions insulin sensitive types, whereas Wilkins, Fleischmann and Block (22) have drawn attention to the prevalence of thyroid sensitive types as measured by the serum cholesterol and the creatinine excretion. It is likely that when techniques are perfected it may be possible to assess the sensitivity to other hormones. So far Gillman (12) has shown that some women are more sensitive to progesterone than others as measured by the effect on the menstrual cycle. The subjective reactions induced with progesterone also indicate that some women have stable autonomic and vasomotor systems, whereas others are unstable as it has been possible to produce a condition simulating premenstrual tension with 30 mg. of progesterone in one woman; other women injected with the same quantity of progesterone exhibited no untoward reactions even though their cycles were as profoundly disturbed as the one who experienced violent subjective reactions (23). Frank (24) refers to 'labile' types of women in respect of the subjective reactions experienced by women in the premenstruum.

The evidence presented above indicates that women exhibit different degrees of resistance to estrogen and in this confirms in a factual manner the claims made by many clinicians of the existence of endocrine types. The technique for assessing estrogen sensitivity is simple and will certainly find clinical application.

As with all tests of this character, difficulty arises as to what can be regarded as normal and what are to be the limits of normality. This can only be established after large groups of women are examined. The classification submitted above in respect to estrogen sensitivity is necessarily only arbitrary and will possibly need modification as additional data become available. This study at least demonstrates that women may be resistant or sensitive to estrogen and the suggested technique forms a basis, flimsy though it may be, for arriving at an appreciation of the degree of resistance or sensitivity that women may show towards estrogen.

Clinical Significance of Experiments with Estradiol in Women

Postponement of the menstrual cycle. Estrogen has been used to postpone the onset of the menstrual cycle. Foss (2) has recommended for this purpose the repeated administration of large quantities of estrogen commencing in the first half of the cycle. There is no doubt that this purpose can be achieved provided adequate quantities of estrogen are used; the exact amount will obviously depend on the degree of sensitivity to estrogen of the women concerned. If the cycle is postponed there seems little doubt that this is achieved by inhibition of the ovaries, and this inhibition is maintained for as long as the estrogen is administered. When treatment is suspended estrogen withdrawal bleeding supervenes after the usual latent period of 5 to 11 days. When enormous doses of estrogen are used hyper-estrogen bleeding may be provoked and the object of postponing menstruation is defeated. It is difficult to assess offhand what is an enormous dose of estrogen, because of the varying degrees of individual sensitivity to this hormone. For one woman 0.5 mg. may be relatively enormous, whereas for another 5 mg. may be scarcely adequate.

If estrogen treatment is continued over a period of several weeks all of the follicles in the ovary may be destroyed as Zondek showed in the human female and a Gillman demonstrated in the baboon. Both of these observations show definitely that exogenous estrogen has a profound effect on the ovary, albeit of a temporary nature.

Of course, if the estrogen metabolism is delicately regulated, estrogen used empirically may have a serious effect. This we have observed clinically when the administration of 1 mg. of estradiol benzoate for 7 days actually induced amenorrhoea for several months and during this period there was no evidence of ovarian activity. On the other hand in resistant women large quantities of estrogen may affect the cycle in question, but thereafter the normal menstrual rhythm becomes rapidly established. In baboons 75 mg. of estradiol given over a period of 67 days produced scarcely any alteration in the cycle succeeding the experimental one (25). Apparently such huge amounts and even larger may not deleteriously influence subsequent cycles in women (26). These experiments show, then that estrogen given in the first part of the cycle produces ovarian inhibition.

Intracyclic hemorrhage. Zondek and Rozin (13) induced intermenstrual bleeding in women to whom 50 mg. of progesterone had been given. Such bleeding was called "intracyclic bleeding." At about the same time Gillman showed that within 4 to 5 days after the administration of an adequate dose of

progesterone in the first part of the cycle, bleeding could be induced in normal female baboons. In this way the cycle could be shortened by more than half of its normal length. Later it was shown that in women intracyclic hemorrhage could not be consistently produced with progesterone although the cycle could be shortened (12). It was suggested that bleeding in or near the middle of the cycle might be due to a sudden formation of a progestogen attended by an equally sudden diminution thereof (12).

It seems possible now that a sudden increase in the production of estrogen might so inhibit the ovaries as to cause atresia of the follicles attended by a sudden decrease in estrogen and the onset of estrogen withdrawal bleeding some days later. Thereafter the ovary may recover slowly, but only for a few days and since the stimulus for the production of estrogen may be weak, the ovary fails, and consequently bleeding may supervene once more as happened in *case* 9 where two bleedings occurred within one month.

Mid-cycle hemorrhage may now be due to abnormal progestogen or estrogen metabolism. Apart from the two possible causes of this condition already mentioned, it has been rightly or wrongly suggested on many occasions that such bleeding in the human female and in monkeys near the middle of the cycle may be an indication that ovluation has taken place.

The prolonged cycle. It is a common enough experience in clinical gynecology to find women who menstruate normally every 28 days and then for some unknown reason they will experience at 44 to 50-day cycle. Thereafter such women menstruate regularly again. Such a delayed cycle is regarded as a missed cycle. Again there are other women who one month may have a 17 to 19-day cycle and the next a 40 to 50-day cycle. The cause of such disturbances has not hitherto received any satisfactory explanation.

It was shown that a single or a double injection of a total of 20 mg. of progesterone given to women on the 8th day of the cycle is capable of delaying the onset of menstruation for as much as 15 days (12). From this it follows that the sudden production of a progestogenic substance in the first part of the cycle is capable of upsetting the ovarian rhythm sufficiently to delay the onset of menstruation for a considerable time.

Similarly it has been shown that 5 mg. of estradiol benzoate administered on the 8th day of the cycle can delay the onset of menstruation for 16 days (*case* 4) or even as long as 20 days (*case* 2). This delay, it is suggested, has been caused by inhibiting the growth of the Graafian follicles for a considerable period and thereafter an almost new cycle is initiated, without the intervention of estrogen withdrawal bleeding. It is more than likely that in such cases ovulation is postponed and that bleeding does eventually take place from a progestational endometrium.

Where such delayed cycles are encountered in women it might be due either to the prococious elaboration of progestogen as mentioned above or to an excessive formation of estrogen, and this estrogen either directly or indirectly causes follicular atresia which in turn lowers the estrogen threshold for a variable period of time and thereafter the follicles begin to ripen and are able to develop normally. Thenceforth the sequence of events is similar to that which obtains in a normal cycle, except, naturally, that the onset of menstruation is significantly delayed.

The shortened cycle again may be due either to the presence of progestogen as shown in a previous study (12) or else excessive estrogen in a sensitive woman may cause such profound ovarian inhibition that recovery of the follicles is delayed so long that the estrogen falls below the threshold and bleeding is precipitated as described for *cases* 1, 3, 8, 9, 21 (table 1). In the succeeding cycle it is possible that there may be once more a sudden production of estrogen but in this instance the inhibition is not sufficiently extensive to cause estrogen withdrawal bleeding but adequate partially to inhibit the ovaries and so lead to a slight or excessive prolongation of the cycle. In this fashion a short cycle may alternate with a long one. Examination of the endometrium in the shortened cycle may then show the absence of a progestational reaction but a progestational endometrium will be encountered most probably at the end of a delayed cycle. These experiments with estrogen in women afford valuable information concerning the nature of the mechanism which may lead to aberrations of the normal cycle.

Estrogen and dysmenorrhea. Two women (*cases* 8, 21) normally suffered from severe dysmenorrhea, but they reported that when they bled prematurely following the estrogen treatment such bleeding was unattended by the violent pain which accompanies the normal periods. Since in these two instances the experimentally induced bleeding was most likely of the estrogen withdrawal variety, it seems likely that the dysmenorrhea in these cases must be associated with some abnormality in the progestogen metabolism. While this observation does not in any way materially assist in solving this vexed problem it does at least indicate that temporary relief may be given to some women by the administration of estrogen in the first part of the cycle. To these women even this temporary relief may be most welcome.

Inhibition of ovulation. Ball and Hartman (5) have shown that estrogen inhibits ovulation in the Macacus rhesus. It has been demonstrated that a

single injection of estrogen also postpones ovulation in the baboon (11). From the experiments reported above it is more than likely that estrogen also postpones ovulation in a number of women especially in those in whom the cycle was significantly lengthened or shortened. That estrogen can inhibit ovulation is evident from the observations of Zondek (1) in the human female and from those of Gillman in the baboon in which the daily treatment with estrogen causes massive atresia of the follicles (11) and even atrophy of the ovary (1). When for some reason it is desirable to inhibit ovulation, there is no doubt that continuous treatment with adequate amounts of estrogen will most certainly achieve this purpose.

Clinical assessment of the estrogen activity of the ovaries. Perhaps the most important contribution emerging from this investigation is that it is possible without complicated laboratory procedure to obtain some indication of the functional activity of the ovaries in respect to estrogen. Since the time it was first shown that disturbances in the estrogen metabolism may seriously impair the normal menstrual cycle tireless efforts have been made to discover some method whereby this metabolism of estrogen could be satisfactorily estimated in women with normal and abnormal cycles. To this end the numerous methods for estrogen assay have been introduced. Unfortunately however, the biological assays for estrogen are both tedious and costly, and do not readily allow of their use by clinicians who have no laboratory facilities. What is more important, appraisal of the results of such assays can hardly be possible without accepting the existence of estrogen-sensitive and estrogen-resistant types of women.

Before such a biological test can be satisfactorily applied it follows that much more information must be made available concerning the range of variation of estrogen levels in so-called normal women. Otherwise a result may be obtained which may be regarded as normal for one woman but which is definitely abnormal for another.

The experiments in women recorded above indicate definitely that some women are more sensitive to estrogen than others. There can be no doubt that there is a measurable difference of the estrogen sensitivity of *cases* 7 and 9. A careful followup of these two women over the next 10 years may provide extremely interesting information, as it may be possible that these two women may develop different kinds of endocrine disturbances, or one may continue to have normal cycles throughout her life and the other may later develop an abnormal cycle. It seems scarcely credible that such a discrepancy in the reactions to the same amount of exogenous estradiol represents the two extremes of normality. If a sufficiently large number of women tested with estrogen in the manner indicated can be followed over a number of years and a correlation can be established between the degree of estrogen-sensitivity and the susceptibility or resistance to disease it may then become possible to prognosticate the tendency towards disease in socalled normal women. This aspect of gynecology has not yet received sufficient attention but it seems that this approach may yield fruitful results.

SUMMARY AND CONCLUSIONS

Estradiol benzoate administered as a single injection to women in the first part of the cycle causes significant alterations in the normal sequence of the menstrual rhythm. Depending on the amount of estradiol and on the sensitivity of each woman, estradiol led to marked shortening of the cycle which was reduced in length by 8 to 11 days; the cycle was greatly lengthened when menstruation was delayed for 16 to 20 days, or, again, the cycle was lengthened by 3 to 8 days.

In one case intracyclic hemorrhage was produced with 1 mg. of estradiol such as occurs in some women after treatment with progesterone.

The reactions of the human female to estradiol benzoate are in general similar to those of the baboon under similar experimental conditions, except that in the baboon it has not been possible to induce intracyclic hemorrhage as occurred in one woman; it is also much more difficult to produce a shortened cycle in baboons than in women.

The alterations in the human menstrual rhythm after estradiol are regarded as being due to interference with the normal ovarian rhythm, since in baboons, the administration of estradiol in a single injection causes massive atresia of all the large and medium sized Graafian follicles. Owing to the similar alterations in the cycle of the baboon and woman after estradiol, it is suggested that follicular atresia also occurs in woman.

The greatly shortened and the greatly lengthened cycle in women are regarded as being almost similar reactions, except that in the former, after a period of ovarian inhibition the estrogen threshold is lowered to such an extent that bleeding supervenes, whereas in the latter the ovary recovers before the bleeding threshold is reached and an almost normal cycle follows the inhibited one. The slightly shortened cycle is evidence of partial ovarian inhibition produced in the same way as in baboons.

By using as an indicator the disturbance in the length of the cycle, it is possible to calibrate the production of estrogen by the ovary against known quantities of exogenous estradiol. It is suggested that the much shortened or the much lengthened cycle

after estrogen treatment implies that there is total ovarian inhibition and therefore the amount of estrogen formed by the ovaries is less than the equivalent of the exogenous estrogen.

By grading the responses of women to the same and different amounts of estradiol it has been possible for the first time to present definite evidence for the existence in women of estrogen-sensitive and estrogen-resistant types. This emphasizes once more that every case must be assessed, and that it is impossible to generalize concerning types of grades of response.

On the basis of the facts presented, it is shown that the postponement of menstruation induced by the repeated administration of estrogen commencing in the first part of the cycle is due to ovarian inhibition and that bleeding will occur within 5 to 11 days after cessation of treatment. Such bleeding is regarded as of the estrogen withdrawal variety. The success which attends efforts to postpone menstruation is dependent on the quantity of estrogen used and this in turn is determined by the degree of estrogen-sensitivity of each woman.

Estradiol benzoate used in the manner described can postpone ovulation. It has been shown that intracyclic bleeding may be produced by estrogen as well as progesterone. The causation of intracyclic hemorrhage is briefly discussed.

The problem of the shortened or the prolonged cycle is briefly reviewed and the causation of such cycles is examined in the light of the experimental data presented in this study on women.

Attention is drawn to the technique now available for assessing the estrogen activity of the ovaries and it is suggested that it might be possible by careful followup to discover whether the estrogen-resistant or estrogen-sensitive types are liable to specific gynecological pathologies.

I wish to acknowledge my gratitude to those women who so willingly collaborated in this investigation. My thanks are due to Professor R. A. Dart for his continued encouragement.

This investigation was aided by a grant made by the National Research Grant Board (South Africa).

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The Nature of the Subjective Reactions Evoked in Women by Progesterone with Special Reference to the Problem of Premenstrual Tension[1]

[Premenstrual Tension]

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IT HAS BEEN KNOWN for many years that emotional states and mental and physical efficiency of women fluctuate very considerably during the menstrual cycle. Ellis (1) has summarized in a masterly fashion the literature relating to this subject. The social implications of these collective observations have not been sufficiently appreciated in regulating the activities of women in industry and in other potentially hazardous occupations. Frank (2) has drawn attention to the severe handicaps experienced by some women in the premenstruum. These may become so grave as to necessitate drastic treatment by temporary or even permanent inactivition of the ovaries. Frank thought that these disturbances were associated with an overproduction of estrogen and its defective excretion. Later Israel (3) tentatively concluded that premenstrual tension was due to defective luteinization or relative hyperestrogenemia and he therefore suggested the use of corpus luteum to alleviate this condition.

In a recent paper it was shown that progesterone administered to women in the first part of the cycle caused significant alterations in the menstrual rhythm, in the same manner as demonstrated in baboons (4, 5). Apart from the disturbances in the cycle evoked during these human experiments, many of these women experienced a variety of subjective reactions simulating so closely those usually encountered before menstruation and even in premenstrual tension that it seemed sufficiently important to merit record.

OBSERVATIONS

The subjective reactions experienced by the women who formed the subjects of this experiment are given in the following short protocols. In table 1 details of the day of the cycle on which the progesterone was administered together with the number of injections, the total amount of progesterone and the effect on the length of the cycle, are briefly summarized.

Cases 1 and 2. These two women experienced no noticeable reactions except that one of them complained of a slight 'menstrual pain,' which came on 24 hours after the injection and passed off within a few hours.

TABLE 1. EFFECT OF PROGESTERONE ON THE LENGTH OF THE HUMAN MENSTRUAL CYCLE

Case No.	Day of cycle injection(s) given	Total amt. progesterone	Length of normal cycle	Length of experimental cycle
		mg.	*days*	*days*
1	8	10	26	26
2	8	10	26	32
3	8	15	29	29
4	8, 10	15	29	29
5	8	20	25	13[1]
6	8	20	31	42
7	8, 11	20	31	46
8	8, 12	20	29	29
9	8, 10	20	30	13
10	8, 10	20	30	25
11	9, 11, 13	30	28	17
12	8, 10, 12	30	25	15[1]
13	8, 10, 12	30	30	15
14	8, 10, 12	30	28	16

[1] Intracyclic bleeding.

Case 3. On the 10th day of the cycle, i.e., 2 days after the injection, she complained of a severe headache and felt very tired. On the 11th day she suffered severe colicky pain low down in the abdomen at which time thick white mucus appeared and lasted for a whole day. Next day severe abdominal pain lasting for 12 hours recurred.

Received for publication December 27, 1941.

[1] This investigation was aided by a grant from the National Research Grant Board of South Africa.

Thereafter the patient felt very well and did not have any other symptoms even at the onset of her period.

Case 4. Twenty-four hours after the first injection this subject developed an uncomfortable feeling of dryness in the nose similar in many respects to the sensations heralding the common cold. At the same time a severe deep-seated headache developed. On the day of the second injection the patient felt severe pains low down in the abdomen and especially over the sacrum. On the 14th day a thick mucus discharge appeared; this was the first discharge that the patient had ever experienced.

Case 5. On the 10th day this patient experienced an interesting group of reactions. These were severe headache, running eyes and nose. The woman said she had developed a cold without any soreness of the upper respiratory passages or the general malaise which is usually associated with that condition. There were violent abdominal pains on the 10th day and these passed off completely a day later. Although she bled twice in the same month (table 1) the second bleeding which occurred near the normal expected time was unattended by the symptoms experienced after the administration of progesterone.

Case 6. This individual experienced the worst sensations recorded in this series of experiments. A day after the injection she suffered an attack of faintness associated with a cold sweat, marked dizziness and a feeling of 'blackness' in front of the eyes. She became extremely nauseated and her head ached severely. This ache she described as a feeling as if her 'head were gripped in a vice' and it was relieved only after she fainted. On the 10th day of the cycle her nose became dry and she nearly 'sneezed her head off.' The running nose continued for 2 days but there was no pain. Four days after the injection, although the nose was still secreting freely, she no longer felt any lassitude and her general condition improved rapidly. Although her menstrual bleeding was delayed (table 1) she felt no discomfort.

Case 7. This patient experienced nothing abnormal until a day after the second injection when she noticed a thick whitish discharge which lasted for one day.

Cases 8, 9, 10. These women said that they felt nothing unusual after the injection.

Case 11. The patient developed a very irritable throat on the day of the second injection. She felt 'under the weather' and was extremely irritable, so much so that when teased in the office she threw a pot of ink at her provocateur, a thing she had never done before. During this and the subsequent two days she felt very depressed, very unhappy and had several long spells of weeping. Such depression had never been experienced before and she remarked that it was strange as she was perfectly happy and there did not seem to be any exciting cause. On the day of the third injection she developed severe backache which passed off when the experimentally induced bleeding set in.

Cases 12, 13, 14. These patients had nothing of note to report.

DISCUSSION

It is generally accepted that a large number of women experience a varying degree of physical and/or mental incapacity either at or some days preceding the onset of menstruation. Such women as a rule are not sufficiently incapacitated to seek medical advice nor apparently are their daily adjustments of such a complex nature as to precipitate an obvious physical or mental crisis. There are some women moreover who apparently can easily function in an ordinary environment but, when called upon to make a rapid or a spontaneous adjustment during the premenstruum, break down temporarily, sometimes with serious consequences to themselves and even to others.

Whitehead (6) drew attention to a number of serious and fatal accidents among women pilots and later information revealed that many of these accidents occurred at the time when these women were menstruating. Whitehead is of the opinion that there can be no doubt of the relationship between the emotional states and the mentrual cycle. McCance, Luff and Widowson (7) affirmed from their careful examination of a number of women over a period of 6 months that many physical and mental symptoms are obviously and, in some cases, unexpectedly rhythmical; other phenomena show comparatively little periodic variation, whereas many of their results were inexplicable. The symptom-complex described by Frank and called premenstrual tension manifests itself 7 to 10 days before the onset of menstruation in the form of marked physical unrest, great irritability and a desire to find relief by foolish and ill-considered actions. The existence of this clinical condition was later confirmed by Israel.

The etiology of the physical and mental disturbances immediately preceding menstruation is not definitely known. Frank was the first to suggest a hormonal pathogenesis for premenstrual tension. In 'labile' women the excretion of estrogen does not proceed in a normal manner, and in the premenstruum the concentration of the female sex hormone affects the sympathetic and the cardiovascular systems to the extent expressed by the symptoms. On the first day of menstruation Israel (3) curetted 3 of 4 women suffering from premenstrual tension. He found two to be bleeding from an interval and one from a hyperplastic endometrium. In his opinion this seemed to indicate that cyclical bleeding was taking place from an endometrium lacking the secretory influence of the

corpus luteum and therefore either ovulation had failed to take place or else there was a quantitative disproportion in the production of the ovarian estrogen and progestogen. Israel felt in consequence of the histological examination of the endometria in his 3 cases, that premenstrual tension was most probably due to defective corpus luteum activity and that it was plausible to treat such cases with progesterone.

In the experiments recorded above it was seen that in one woman (*case 11*) the administration of 30 mg. of progesterone in the first part of the cycle produced a profound mental effect, almost simulating the picture of premenstrual tension, even to the extent of being dramatically relieved when the uterine bleeding appeared, although in this instance it was precipitated prematurely on the 17th day of the cycle (table 1, *case 11*). Israel's suggestion that premenstrual tension might be due to defective corpus luteum activity receives support from the reactions of *case 11* here reported, but it is hardly likely that it is due to a deficiency. That it is plausible to treat cases of premenstrual tension with progesterone scarcely seems logical, nor is this remark supported by Israel's results in 10 cases, as the administration of corpus luteum cured one and temporarily relieved six; four of the six and two additional patients were subsequently cured by low dose irradiation to the pituitary gland and the ovaries; one malnourished patient was benefited by a gain in weight aided by insulin therapy. This does not seem to be an impressive basis for inspiring the continued use of progesterone in alleviating premenstrual tension.

Apart from the severe mental effect induced in *case 11*, progesterone was responsible for a variety of other symptoms in this and other cases. These and their incidence are shown in table 2.

On analyzing the symptoms (table 2) it is noteworthy that the nose should have been so frequently implicated. This coincidence can hardly be regarded as cogent evidence for the existence of a naso-genital relationship but the possibility cannot be entirely disregarded. On the other hand such reactions may be caused quite easily by a disturbance in the vasomotor mechanism. Of those who complained of headache one patient in particular was of special interest. In this instance (*case 6*) the description of the headache was so unmistakable as to leave little doubt that the pituitary had been affected.

The low abdominal pain, backache, irritability, fainting attacks and vertigo are symptoms which cannot escape emphasis especially as the women were certain that these reactions were never previously experienced in the first part of the cycle. Even before the onset of the normal menstruation those women who complained of those symptoms stated very definitely that the reactions were never so severe as those induced experimentally The fainting attack was the first ever experienced by *case 6*.

On comparing these symptoms with those commonly appearing in the premenstruum, it is at once apparent that they are strikingly similar. Both apparently are probably disturbances of the vasomotor mechanism and of the vegetative nervous system. In the experimental subjects the onset of these symptoms within a day or two after the administration of the progesterone and their sudden disappearance at a time when this hormone has been metabolized affords undeniable evidence that progesterone in sufficient concentration is the exciting cause. Since the menstrual molimina usually disappears with the onset of menstruation or soon after it is suggestive of the possible rôle of progesterone in their production. Obviously progesterone alone is not the only factor as 7 of the 14 women were unaffected.

TABLE 2. SYMPTOMS EXCITED IN WOMEN TREATED WITH PROGESTERONE IN THE FIRST PART OF THE CYCLE[1]

Symptom	Frequency
Rhinorrhoea	5
Low abdominal pain	4
Heacache	3
Malaise	2
Profuse cervical discharge	2
Irritation of the throat	2
Backache	2
Irritability and depression	1
Fainting attack	1
Vertigo	1

[1] Seven women experienced no reactions at all even though in some cases the cycle was profoundly disturbed.

Frank felt that in premenstrual tension not only was a particular disturbance in the secretion of the ovarian hormones necessary, but also that this must take place in a 'labile' woman. Although 'labile' is not a happy term it nevertheless implies that there are women who are much more easily upset by slight deviations from normal activity of the ovaries than others. This is clearly demonstrated in the above experiments with progesterone and experiments of a similar nature with estradiol benzoate (8) go to prove the same point. It follows that the symptomatic responses to progesterone will depend on the degree of sensitiveness of the nervous system of each woman to this hormone. Some women will be profoundly affected by a relatively small dose, whereas others even after very large doses feel no ill effects.

This variation in the susceptibility of the nervous system to hormones in supposedly normal women is obviously important, but the knowledge is somewhat lessened in the absence of sufficiently reliable tech-

nics for assessing this stability in each woman. The assay of the ovarian hormones or their derivations in blood and urine is obviously an important step in that direction, but quantitative assays (at present a laborious process) so far alone have not proved to be as valuable as anticipated since there are a host of unknown problems in connection with the metabolism of the hormones and the state of the nervous system which do not allow of a satisfactory interpretation of the findings. In the meantime it seems that the judicious and controlled administration of hormones in one or other part of the cycle together with a careful follow-up of the reactions elicited may afford some indication, crude as it may be, of the degree of sensitiveness of the nervous system. For example, if we examine the effects of 30 mg. of progesterone (*cases 11, 12, 13, 14*, table 1) we see that the subjective reactions in *case 11* were very severe, whereas in the others they were not sufficiently marked to merit any attention. Although *case 11* in ordinary circumstances can be regarded as normal it is quite obvious that if here endocrine balance should become disturbed by an abnormal production of progestogen she might be destined to suffer from premenstrual tension. Such a woman employed in a dangerous occupation (pilot, industrial worker) under certain circumstances outside her control, may become a menace to herself and even to others.

It is evident, moreover, that a disturbed menstrual cycle is not necessarily attended by symptomatic reactions, as in *cases 11, 12, 13, 14* the menstrual cycles were altered in more or less the same fashion and yet *case 11* was the only one to experience severe reactions; the others were completely unresponsive. Again, the severity of the symptoms or even their presence is not dependent on the amount of progesterone since 30 mg. progesterone excited no reactions in *case 12, 13, 14*, whereas 15 mg. was able to incapacitate a woman by causing a severe headache and violent abdominal pains (*case 4*). Just as it was shown in a previous investigation that women vary considerably in their ability to prevent progesterone from upsetting their menstrual rhythm (5), so too, it transpires, that women vary considerably in the way they react subjectively to the same hormone. There is thus a considerable fluctuation both in the stability of the endocrine balance and in the sensitiveness of the vegetative nervous system of different women although it may be constant in each woman. A thorough appreciation of this variability is of the utmost importance, for on this depends, not only the manner in which we treat aberrations of the menstrual cycle, but also, the extent to which we shall be able to prognosticate the tendency towards disease of so-called normal women.

SUMMARY

By using progesterone it has been possible in the first part of the cycle to produce in one woman a condition simulating premenstrual tension and in others reactions similar to those encountered in the premenstruum.

The subjective reactions elicited are not necessarily associated with disturbances of the menstrual rhythm and vice versa.

Not all women are affected in the same way by progesterone, nor is the extent of the reaction dependent on dosage.

The appreciation of the existence of individual sensitivity to hormones is of the utmost importance in determining treatment of menstrual disturbances and in the prognostication of the tendency towards disease in so-called normal women.

I wish to record my thanks to Professor Raymond A. Dart for his advice and encouragement.

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Skin Reactivity during the Menstrual Cycle

[Menstrual Cycle and Allergy]

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Clinical experience has suggested that menstruation influences the state of hypersensitiveness. The effect of the reproductive function on the skin is illustrated by the pigmentation and growth of hair which occur during puberty and pregnancy. Furthermore, a number of cutaneous anomalies and changes are thought to be associated with the menstrual cycle (1, 2). Herpetic lesions are so common during menstruation (3) that a special form of this eruption is recognized as herpes menstrualis. It has been suggested that allergy plays a rôle in this types of herpes (4). Acne is frequently observed in girls at puberty and is accentuated during menstruation. Unusual sensitivity to light on the first and, at times, on the second day of menstruation has also been described.

In regard to allergic phenomena, urticaria, angioneurotic oedema and various forms of diffuse or circumscribed erythemas have been reported as occurring only during menstruation and pregnancy. It has also been suggested (5) that most instances of tuberculin allergy in females coincide with some phase of active ovarian function.

The problems of allergy and immunity are closely related. In recent years there have been a number of investigations of the relationship of menstruation and the estrogenic cycle to natural and acquired resistance. It has been shown experimentally that certain sex hormones can change the tissues and thereby alter their resistance to infection (6). The estrogenic hormone slows up and reduces the spread of India ink in the skin of rabbits, and increases their resistance to vaccinia (7); the same obtains as the result of pseudopregnancy (8, 9). It is believed (10) that a rise of the estrogenic hormone level in the blood is accompanied by stimulation of antibody-forming cells. However, it has been pointed out that the apparent increased resistance to infection during menstruation may well be due to changes in the physical properties of the serum (11); it is not necessarily an index of systemic resistance to infection.

Observations in regard to skin reactivity during menstruation are somewhat vague. It has been mentioned that there is an increase in susceptibility of the skin to local virus and bacterial infection. Some investigators state that the autonomic tone of the cutaneus capillaries is changed during the premenstrual and early menstrual period (12), and renders such capillaries more permeable (13).

The impression that "A state of hypersensitiveness is frequently observed in the premenstrual period and the early days of menstruation" (14) is based on clinical assumptions rather than on concrete evidence. For this reason, we undertook the following studies.

Received for publication December 27, 1941.

Methods

Thirty women with a 'normal' menstrual history and who were apparently healthy were selected. Of this group, 10 gave a personal or family history of allergy, 20 were non-allergic. They were skin tested to 10 allergens of proven potency, and to 2 control solutions (saline and beef broth). The allergens were extracts of short ragweed, silk, dust, cottonseed, wheat, monilia, hormodendrum, streptococcus allergen; (erysipelas strain) and staphylococcus toxoid. The extracts were prepared by the Coca method. The test dose was 0.1 cc. or less and the injections were given intradermally. The concentration of the various test solutions was 10 times (for fungi, 100 times) the strength of that used routinely in our clinic. The reactions were read at the end of 20 minutes and again at the end of 24 hours. Since the delayed reactions were inconstant and insignificant, they are not considered in this study.

The skin tests were made 10 days before the expected onset of menstruation, and 4 days and one day before; then again on the last day of menstruation, 4 days and 10 days later. Most of our subjects received a complete set of skin tests through two or more cycles, and in all 320 tests were made. At the same time the following accessory determinations were carried out: R.B.C. counts, hemoglobin content, W.B.C. counts, differential white count, sedimentation rate and Weltmann test (16). As was expected (15) the Weltmann coagulation band remained constant except

in one individual who developed an acute infection. In accordance with previous observers (17, 18) we were unable to demonstrate any significant change in the total counts or the pattern of the curves of red cells and white cells during menstruation; particularly was there no change in the eosinophile count. The sedimentation rate did not vary with any significant constancy.

The tested subjects were divided into the allergic group and the non-allergic group; their ages ranged from 20 to 35 years. Results were considered only if all the tests were made at the respective and specified time intervals. The reactions were accurately measured with a planimeter and recorded in square centimeters.

ANALYSIS OF DATA

Allergic Group

The results in this group are given in tables 1 and 2.

Cutaneous reaction to ragweed pollen extract. Six individuals were completely studied. It is seen in table 1, *a*, that the highest 'spread average' occurred on the last day of menstruation, with another rise in the mid-period.

Reactions to dust extract. This comprised a group of 7 women (table 1, *b*). Again the greatest average spread was observed on the last day of menstruation. This held true in all except in one patient in whom the greatest reaction occurred one day before the onset of menstruation.

TABLE 1. REACTIONS OF ALLERGIC SUBJECTS TO ALLERGENS AT SPECIFIC INTERVALS IN THE MENSTRUAL CYCLE

Values are area of wheal, in sq. cm., after 20 minutes

Patient	Time of Cycle with Reference to Menstruation					
	Days before catamenia		Catamenia		Days after end of catamenia	
	10	4	1	last day	4	10
a. Reaction to Ragweed Pollen Extract						
McC. J.	7.5	5.2	4.5	16.5	4.5	5.5
L.S.	13.2	2.2	1.8	12.6	10.9	13.8
P.Y.	3.4	2.2	1.3	5.4	2.3	3.4
D.R.	11.1	5.6	5.3	12.6	5.3	9.5
McR. M.	9.8	13.6	8.5	10.4	17.4	18.7
M.S.	20.9	13.3	15.9	22.0	14.2	17.5
Aver.	10.9	7.0	6.2	14.9	9.1	11.4
b. Reaction to Dust Extract						
McC. J.	8.3	11.7	7.2	12.6	10.6	9.8
L.S. (1)	15.4	2.3	14.7	11.5	3.2	11.9
(2)	14.8	1.9	10.5	14.8	1.2	12.8
D.R.	10.9	13.1	7.8	4.5	5.7	2.7
McR. M.	12.3	6.5	14.5	11.3	7.2	9.3
C.N.	2.1	0.8	1.1	3.2	0.8	1.5
M.S.	8.7	8.1	11.4	12.5	6.5	7.6
Aver.	10.3	6.3	9.7	10.0	5.0	7.9

TABLE 1—*Continued*

Patient	Time of Cycle with Reference to Menstruation					
	Days before catamenia		Catamenia		Days after end of catamenia	
	10	4	1	last day	4	10
c. Reaction to Silk Extract						
McC. J.	8.1	5.3	4.7	4.5	8.3	9.9
R.R.	11.1	8.5	8.8	8.7	5.9	8.1
C.N. (1)	10.5	14.3	5.2	9.8	9.6	13.1
(2)	13.5	14.3	16.7	15.7	13.9	16.5
M.N. (1)	4.5	2.8	3.2	9.5	2.5	2.9
(2)	6.7	3.2	6.6	8.9	2.9	8.7
Aver.	9.0	8.0	7.5	9.5	7.1	9.8
d. Reaction to Wheat Extract						
McC. J.	15.5	2.6	3.2	7.3	9.1	7.6
L.S. (1)	2.4	3.5	4.1	6.3	1.5	2.4
(2)	3.4	2.9	2.8	5.7	3.4	3.4
D.R.	5.7	5.7	4.9	2.4	2.7	6.3
McR. M.	14.0	10.1	11.8	11.0	9.2	12.4
C.N. (1)	10.6	5.5	3.9	12.4	11.3	6.9
(2)	8.9	13.2	11.5	14.9	14.3	8.1
M.N.	7.2	2.3	5.7	2.1	4.8	8.7
M.S.	12.1	12.1	13.5	15.1	12.9	11.5
Aver.	8.8	6.4	6.8	8.6	7.6	7.4
e. Reaction to Staphylococcus Toxoid						
McC. J.	8.3	6.2	3.2	13.0	9.7	6.1
C.N.	10.5	4.0	3.9	5.0	6.2	4.6
M.N.	4.7	1.5	2.2	6.3	5.2	10.5
D.R.	7.7	4.5	3.2	7.8	2.7	3.2
R.R.	3.2	6.0	7.9	6.5	4.9	3.2
L.S.	6.2	3.8	7.0	8.3	4.0	9.3
P.Y.	3.7	3.6	1.2	4.5	2.0	3.8
McR. M.	23.6	5.4	4.5	1.4	0	7.5
R.R.	10.3	11.0	8.7	6.3	8.5	8.8
M.S.	6.7	8.9	12.2	14.9	8.9	7.1
Aver.	8.4	4.7	5.4	7.5	5.2	6.4
f. Reaction to Streptococcus Allergen						
McC. J.	7.7	5.4	4.2	12.0	4.3	10.5
L.S.	2.2	1.4	1.5	2.6	1.3	1.5
D.R.	9.6	6.2	9.5	7.9	5.6	7.3
McR. M.	9.9	7.9	5.3	8.0	6.9	7.8
C.N.	3.3	4.2	3.1	4.5	1.2	2.3
R.R. (1)	1.0	0.8	2.2	4.4	3.6	3.2
(2)	4.9	1.1	3.1	5.7	1.9	2.0
M.S.	7.9	12.0	13.7	14.8	5.3	6.2
Aver.	5.8	4.9	7.0	7.5	3.7	5.1
g. Reaction to Monilia Extract						
McC. J.	3.9	4.8	4.2	11.0	6.0	9.3
L.S.	6.6	12.0	6.3	8.9	3.7	12.9
M.S.	6.6	9.9	13.9	13.8	11.7	7.8
D.R.	1.9	1.0	2.3	4.8	1.4	3.7
McR. M.	12.9	10.1	6.3	6.8	4.5	7.3
C.N.	7.8	4.3	3.9	8.2	1.3	6.5
R.R.	3.4	2.9	2.5	3.5	1.6	9.7
Aver.	6.1	6.4	5.6	8.2	4.1	8.1

TABLE 2. SUMMARY OF AVERAGES (IN SQ. CM.) OF REACTIONS OF ALLERGIC SUBJECTS TO ALLERGENS

Allergen	Time of Cycle with Reference to Menstruation					
	Days before catamenia		Catamenia	last day	Days after end of catamenia	
	10	4	1		4	10
Dust	10.3	7.0	9.7	10.0	9.1	7.9
Monilia	6.1	6.3	5.6	8.2	5.0	8.1
Ragweed	10.9	8.0	6.2	14.9	3.7	11.4
Silk	9.0	6.4	7.5	9.5	7.6	9.8
Staph. toxoid	8.4	4.9	5.4	7.5	7.1	6.4
Strept. allergen	5.8	6.4	7.0	7.5	4.1	5.1
Wheat	8.8	4.7	6.8	8.6	5.2	7.4
Aver.	8.4	6.2	6.9	8.9	5.9	8.0

Reactions to silk extract. The results in 6 individuals are recorded in table 1, *c* for this group. The greatest reactions occurred on the last day of menstruation. The fact that in two individuals the reactions in the premenstrual period were quite marked makes the variation in the average less striking.

Reactions to wheat extract. Nine women were studied in this group data for which are given in table 1, *d*. Again the greatest reactions were observed in all but two individuals during the last day of menstruation. In one (*C.N.*) the variation in the size of reaction of the test made on the last premenstrual day as compared with the reaction obtained on the last menstrual day, exceeded 8 sq. cm.

Reactions to staphylococcus toxoid. This comprised a group of 10 women (table 1, *e*). The greatest reactions were obtained in the mid-period and on the last day of menstruation, except in two patients who gave the largest reaction on the last premenstrual day.

Reactions to streptococcus allergen (erysipelas strain). This group comprised 8 women (table 1, *f*). In this group the average rise of the reaction was greatest on the last day of menstruation, but varied only in less than ½ sq. cm. from that obtained on the last premenstrual day. Furthermore, the average size of the reaction in the mid-period was decidely less than would be expected.

Reactions to monilia extract. Seven women were tested in this group, data for which are in table 1, *g*. It can be seen that the reactions to monilia extract were greatest on the last day of menstruation with a secondary accentuation in the mid-period. This was a constant finding in all individuals of this group.

Summary of results in allergic subjects. The data in table 2 exemplify that the greatest reaction was obtained on the last day of the menstruation with a definite rise in the mid-period. The smallest reaction occurred on the fourth premenstrual day.

Non-allergic Group

A larger number of women were included in this classification, data for which are given in tables 3 and 4.

Reactions to ragweed pollen extract. Only 6 of 20 women gave a positive reaction on one or more occasion (table 3, *a*). It can be seen that the reactions as a whole were relatively slight. Again the maximum reactions were noted on the last menstrual day, the smallest average reaction on the last premenstrual day.

Reactions to dust extract. This group comprised 10 women (table 3, *b*). The results were quite similar to those obtained with ragweed. The reactions tended to be greater than with this pollen.

TABLE 3. REACTIONS OF NON-ALLERGIC SUBJECTS TO ALLERGENS AT SPECIFIC INTERVALS IN THE MENSTRUAL CYCLE

Values are area of wheal, in sq. cm., after 20 minutes

Patient	Time of Cycle with Reference to Menstruation					
	Days before catamenia		Catamenia	last day	Days after catamenia	
	10	4	1		4	10
a. Reaction to Ragweed Pollen Extract						
M.L.	2.4	2.9	1.2	3.8	1.3	2.2
C.N.	4.2	4.7	1.3	5.5	2.2	4.3
S.D.	0	0	0	1.9	0	0.8
P.E.	0	0	0	3.7	1.2	1.8
P.	4.0	1.2	2.5	5.6	2.5	3.7
H.D.	2.6	2.0	1.8	4.5	3.0	3.6
Aver.	2.2	1.8	1.1	4.1	1.7	2.5
b. Reaction to Dust Extract						
P.	3.0	2.4	2.6	4.3	1.8	3.2
P.E.	3.6	1.8	1.5	4.5	4.1	4.0
S.D.	1.2	0.8	1.6	1.2	1.6	1.3
H.D.	5.7	4.8	5.0	5.6	3.8	5.0
D.D.[1]	17.3	7.3	6.7	7.6	13.7	12.1
D.R.	1.0	1.6	1.2	2.5	0.9	1.1
M.L.	9.3	7.1	8.8	9.7	9.3	9.8
N.M.	1.8	0.9	1.3	2.2	1.0	1.6
C.N.	3.6	2.2	4.4	4.4	8.7	4.6
K.	1.6	1.4	2.2	4.3	1.8	2.0
Aver.	4.8	2.5	3.5	4.6	4.6	3.9
c. Reaction to Silk Extract						
D.D.	16.6	12.8	15.9	18.7	15.6	11.7
H.D.	7.8	9.8	8.2	19.4	12.0	5.5
Aver.	12.0	11.3	12.0	19.5	13.3	8.6
d. Reaction to Wheat Extract						
D.D.	18.0	9.1	10.8	10.3	12.0	14.3
M.L.	12.4	12.8	9.3	13.2	9.7	12.1
N.M.	4.1	1.8	1.5	2.7	1.3	3.8
C.N.	12.3	19.6	17.3	22.6	14.0	18.6
P.M	3.3	3.0	4.2	6.8	5.2	3.1
H.D.	7.8	10.9	7.6	11.6	7.5	6.8
S.D.	2.0	0.9	1.2	5.4	1.6	1.8
P.E.	2.0	1.2	2.4	4.2	2.6	1.6
Aver.	7.7	7.4	6.8	9.6	6.7	7.8

TABLE 3—*Continued*

Patient	Time of Cycle with Reference to Menstruation					
	Days before catamenia		Catamenia		Days after catamenia	
	10	4	1	last day	4	10
e. Reaction to Staphylococcus Toxoid						
D.D.	4.4	4.0	3.4	4.4	4.6	3.7
B. El.	4.1	11.6	3.5	7.2	4.9	3.7
B.R.	5.6	8.3	2.4	6.1	2.1	7.3
B. Ev.	9.0	7.2	5.9	5.7	3.8	7.0
P.	3.2	1.8	1.2	3.3	1.7	3.5
M.L.	6.9	2.2	1.8	3.7	5.2	6.4
N.M.	7.9	6.6	5.0	8.4	5.3	6.4
C.N.	7.0	6.1	5.7	16.3	13.4	6.2
B.S.	16.7	2.3	4.2	6.5	4.2	10.7
P.M.	3.8	1.5	1.4	9.1	4.9	4.3
M.P.	4.7	7.0	6.9	9.0	5.7	5.7
K. Mrs.	8.1	10.2	6.4	8.0	6.3	6.9
J.G.	2.4	1.8	2.8	7.2	4.7	4.9
H.D.	4.5	8.6	3.2	6.9	5.9	3.8
W.E.	7.0	6.1	5.2	4.8	3.3	5.3
B.M.	4.2	7.1	5.2	7.7	4.3	3.6
S.D.	5.9	11.3	9.0	6.0	3.6	5.3
P.E.	9.6	7.0	2.7	9.8	5.5	4.4
Aver.	6.3	6.1	4.2	7.2	4.9	5.5
f. Reaction to Streptococcus Allergen						
D.D.	1.2	0.9	1.2	4.6	0.6	1.8
B. El.	2.2	8.2	1.2	14.3	4.7	1.8
B.R.		2.5		4.7		6.4
B. Ev.	2.9	1.8	5.3	8.6	1.8	2.5
P.E.	9.6	9.1	5.6	13.6	10.6	11.2
M.L.	1.8	0.9	1.6	2.8	1.5	0.8
M.P.	1.9	1.8	1.6	2.2	1.3	1.6
K.	2.8	1.5	3.4	7.6	6.2	1.1
J.G.	3.0	1.8	1.2	4.6	2.1	3.7
H.D.	2.8	2.6	1.3	6.2	1.9	3.0
W.E.	3.9	5.3	5.9	3.9		6.4
S.D.	6.1	3.5	2.0	9.6	0.9	4.1
P.	5.8	2.1	3.7	5.3	5.0	3.5
Aver.	3.6	3.5	2.8	7.3	3.0	3.9
g. Reaction to Monilia Extract						
D.D.	4.1	3.7	4.2	8.2	4.1	5.2
B. El.	2.7	1.5	1.8	7.6	3.6	4.6
B.R.	2.1	1.3	0.9	1.4	1.5	2.1
B. Ev.	6.3	5.6	7.0	11.3	8.2	5.7
M.L.	6.9	2.2	1.6	3.7	5.2	6.4
C.N.	2.8	1.6	2.4	1.4	2.8	3.2
M.P.	7.9	4.2	4.9	5.2	4.5	5.0
K.	8.0	9.3	5.0	8.7	9.4	7.1
J.G.	7.5	4.6	3.3	8.7	5.8	7.2
H.D.	4.8	9.6	6.2	12.4	10.1	2.5
W.E.	7.6	5.7	4.3	5.7	4.0	6.3
S.D.	1.3	1.1	1.6	4.6	3.1	2.5
P.E.	4.8	7.1	5.8	8.2	6.3	11.2
P.	1.6	2.5	4.7	8.7	3.5	8.6
Aver.	5.6	5.0	3.8	6.9	5.1	5.6

[1] F.H. positive for allergy?

Reactions to silk extract. Only 3 women were included in this group data for which are given in table 3, *c*. The reactions, it will be noted, were all quite large. The largest reaction occurred on the last day of menstruation.

Reactions to wheat extract. Eight women were tested in this group (table 3, *d*). Again the largest reaction was obtained on the last menstrual day. In three instances, the reaction on the fourth day before menstruation exceeded that in the mid-menstrual period.

Reactions to staphylococcus toxoid. This group comprised 18 women (table 3, *e*). Despite individual variations, the average size of the reactions was decidedly greater on the last day of menstruation. In some instances it was four times the size of that obtained on the fourth day before menstruation or on the last premenstrual day.

Reactions to streptococcus allergens (erysipelas strain). This is a group of 13 women in whom at least one full series of tests could be completed (table 3, *f*). In this group of non-allergic women the reactions to this test substance were decidedly larger on the last day of menstruation, as compared to the relatively slight average reaction on the last premenstrual day.

Reactions to monilia extract. Fourteen women were studied in this group.

Table 3,g shows that the largest reactions occurred on the last menstrual day, but the variation is not very striking.

Summary of results in non-allergic subjects. When the reactions obtained in all patients are grouped as in table 4 the average size of reaction is again largest on the last day of menstruation. It is smallest on the last premenstrual day. There is an increase in the size of the reaction in the mid-period of the cycle.

DISCUSSION

An analysis of these tables shows that the largest average reaction occurred, as a rule, on the last day of menstruation. The smallest reaction was observed on the last premenstrual day. The next largest reactions were found in the mid-period of the menstrual cycle. If the averages are plotted in the form of a curve, the tracings in figure 1 are obtained. It will be seen that the variations in the size of the reaction, and particularly the increase of the reaction on the last menstrual day, were particularly striking when ragweed pollen

TABLE 4. SUMMARY OF AVERAGES (IN SQ. CM.) OF REACTIONS OF NON-ALLERGIC SUBJECTS TO ALLERGENS

Allergen	Time in Cycle with Reference to Menstruation					
	Days before catamenia		Catamenia		Days after end of catamenia	
	10	4	1	last day	4	10
Dust	4.8	2.5	3.5	4.6	4.6	3.9
Monilia	5.6	5.0	3.8	6.9	5.1	5.6
Ragweed	2.2	1.8	1.1	4.1	1.7	2.5
Silk	12.0	11.3	12.0	19.5	13.3	8.6
Staph. toxoid	6.3	6.1	4.2	7.2	4.9	5.5
Strept. allergen	3.6	3.5	2.8	7.3	3.0	3.9
Wheat	7.7	7.4	6.8	9.6	6.7	7.8
Aver.	6.0	5.3	4.8	8.5	5.6	5.4

extract was used. Furthermore, the mid-period level of reaction for all three inhalants in the allergic group of subjects was more or less the same.

The reactions to bacterial products (extracts) are plotted in figure 2. In this group the average size of the reactions to the various allergens at the mid-period level varied considerably. The largest reactions were seen on the last menstrual day. The three allergens produced a largest average reaction of almost the same size. There seemed to be no significant difference in the size of reactions during the immediate premenstrual and postmenstrual periods.

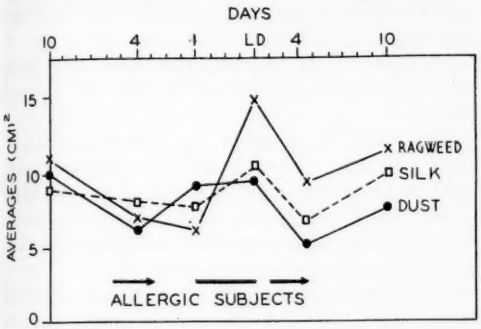

Fig. 1. Allergic response during the menstrual cycle.

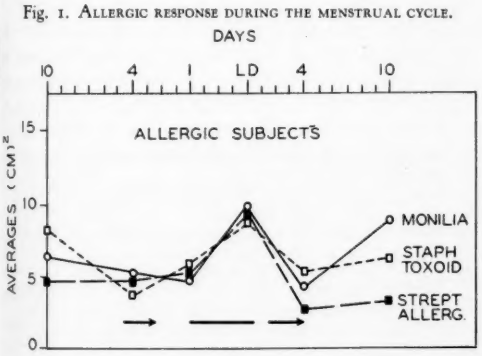

Fig. 2. Allergic response during menstrual cycle.

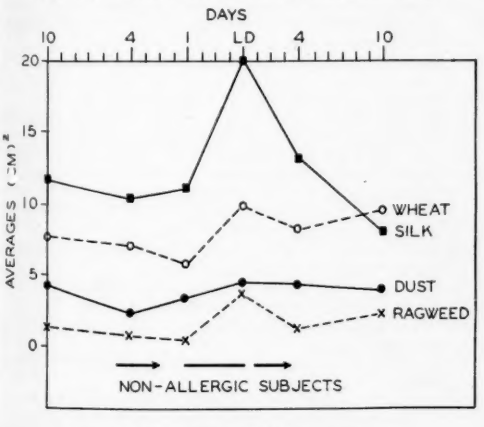

Fig. 3. Response of non-allergic subjects during menstrual cycle.

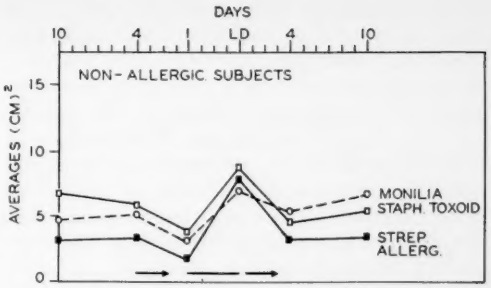

Fig. 4. Response of non-allergic subjects during menstrual cycle.

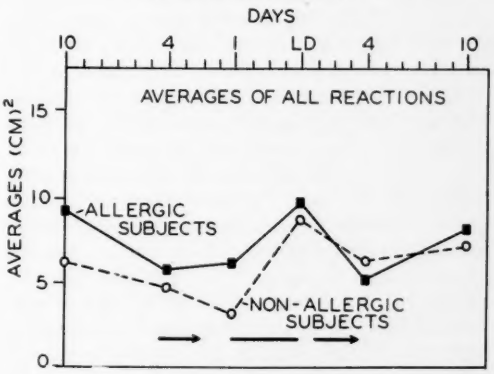

Fig. 5. Response of women to allergens during the menstrual cycle.

In the group of non-allergic subjects, the reactions to inhalants showed relatively little variation in their average size, with the exception of the reactions to silk (fig. 3). The group of individuals tested to silk is rather small, but in all of them by far the greatest reaction occurred on the last day of menstruation. It is, of course, not surprising that the reactions to inhalants in this group were relatively insignificant despite the proven strength of the test solutions.

When the size of the average reactions to bacterial extract is compared, one is again impressed by the constancy with which largest reactions occurred on the last menstrual day. The smallest reactions were seen on the last premenstrual day. In the mid-period the reactions were definitely larger than in the immediate postmenstrual and premenstrual periods.

The average size of the reactions, regardless of the test substance used, was greatest on the last day of menstruation. The differences were more striking in the allergic than in the non-allergic group, and the average size reaction was larger in the allergic individuals.

These studies do not prove or disprove the existence of a greater state of hypersensitiveness during

the premenstrual or early menstrual period. They demonstrate that the skin of women, and particularly allergic women is most reactive during the last day of menstruation and the least reactive in the period immediately preceding menstruation. It has been reported (5) that the same is true of the reaction to tuberculin in women. In contrast with a frequently repeated assumption, the reactivity of the skin of women is least in the late premenstrual phase. It has also been generally assumed that the high tide of circulating estrogenic hormones induces a greater reactivity of the woman's skin. The results of our tests do not bear this out. On the contrary, the largest reactions were obtained on the last day of menstruation, during the end-period of estrogenic deprivation (19). The next largest reactions occurred in the mid-period which corresponds to the time of ovulation.

It is possible that the degree of hydremia and dehydration play an important rôle in determining the size of the skin reaction during the menstrual cycle. As has been shown (21) when the area of spread of a virus in the skin is greater, more cells will come into contact with the virus and hence the greater will be the chance for the appearance of a lesion. It is possible that in women the antigen comes into contact with a greater amount of antibody on the last day of menstruation because of a state of relative dehydration. Reversely, the smaller reactions may well be due to a relative hydremia in the premenstrual period.

As stated before, these observations do not clarify the relationship of the menstrual cycle to hypersensitiveness. Studies are now in progress, using passive transfer tests, which we hope will throw some light on this problem. It can be assumed, however, that a low estrogenic titer invites a larger spread of test allergens in the skin of women. The converse is not necessarily true. We are well aware that endocrinologists may raise the question that our subjects did not necessarily have a normal menstrual cycle. It can only be assumed, since our tested women were all apparently healthy and normal technicians and nurses.

It has already been mentioned that in our cases there was no significant variation in the red cell or the hemoglobin count during the menstrual cycle. This is in agreement with previous observations. Repeated platelet counts were not made, but fresh blood preparations stained separately with brilliant cresyl blue were examined frequently when the skin tests were made. A significant variation in the platelet count, such as reported by other investigators (20), was not demonstrated.

SUMMARY AND CONCLUSIONS

Ten allergic and 20 non-allergic women were tested intradermally to a series of potent allergens in strong solution. These tests were made in the mid-period of the menstrual cycle, four days and one day before menstruation, on the last day of menstruation, four days later and ten days after the end of the menstrual bleeding. At least one complete cycle was covered. The reactions were carefully measured with a planimeter and recorded in square centimeters.

The reactions in the allergic group were as a rule larger than in the non-allergic group. This difference was not so marked when bacterial extracts were used. The largest average reaction was obtained on the last day of menstruation, the smallest on the last premenstrual day. As a rule, large reactions were obtained in the mid-period, but these were all less marked than the reactions obtained on the last day of menstruation.

There was no significant variation in the white blood cell count, red cell count, hemoglobin content, differential white blood cell formula during the menstrual cycle. The Weltmann coagulation band did not vary materially. There was also no demonstrable significant change in the platelet count.

The greatest skin reactivity coincides with the period of estrogenic deprivation. There was also a less marked increase in the skin reactivity during the mid-period, coinciding with the time of ovulation. It is suggested that a low estrogenic titer invites a larger spread of test allergens in the skin of women.

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A Six-hour Pregnancy Test

[Chorionic Gonadotropin]

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THE WORK REPORTED HERE had its origin in a series of studies designed to determine how soon after the administration of gonadotropic hormone, gonadotropic effects could be detected in the immature rat ovary. In a study of the time factor relationship of follicle stimulation to luteinization in the immature rat, several years ago, it was noted that "in somea cses the immature rat ovary will respond to gonadotropic hormone with a follicle-stimulating reaction as early as 26 hours after the first injection" (1). In subsequent studies an attempt was made to determine whether it was possible, by increasing the dosage of the gonadotropin, adding hypophyseal synergist or using older animals, to accelerate the gonadotropic action of the extracts. Two observations were made during these studies which suggested their utilization as a test for human pregnancy. These observations are that, *a*), as early as 6 hours after the administration of pregnancy urine to immature rats, one can detect marked hyperemia of the ovaries, and, *b*), by the end of 24 hours one can discern gross and microscopic evidence of estrogenic stimulation of the vagina. It was felt that these reactions which are evoked respectively by the gonadotropic and estrogenic hormones present in pregnancy urine could serve as a rapid dual test for pregnancy, providing for a reading in 6 hours and a supplementary check at the end of 24 hours. To be of practical value as a test, the end-points of these reactions must be easily detectable grossly and consistent in their occurrence.

In order to determine if such end-points could be established, a preliminary series of experiments was performed with urines of normal pregnancies and control urines from nonpregnant individuals. The effects upon the ovaries, uteri and vaginae were studied grossly and microscopically at intervals of 6, 12, 18 and 24 hours after injection. The amount of urine administered varied from 1 to 8 cc. and the animals used varied in weight from 30 to 52 gm. These preliminary studies revealed that at the end of 24 hours the two reactions, ovarian hyperemia and hypertrophy of the vagina, were clearly detectable by the naked eye, but at shorter time intervals, the estrogenic action on the vagina became progressively less marked so that below 12 hours it was not possible to detect gross evidence of the estrogenic effect. The ovarian hyperemia however, was uniformly detectable as early as 6 hours after the injection and in some instances was more striking at 6 than at 12 or 24 hours. It was noted furthermore that varying the dose from 1 to 8 cc. did not appreciably affect the reactions and that variations in weight of the animals from 30 to 52 gm. did not significantly influence either the ovarian or vaginal reactions.

To determine the reliability of these reactions as a test for human pregnancy, we have performed a series of tests of unknowns, comprising urine specimens from women in various stages of pregnancy, as well as from menopausal, amenorrheic and normal cyclical women. The urines were tested by both the 6-hour ovarian reaction and by the 24-hour ovarian and vaginal reactions.

METHODS AND MATERIALS

6-hour test. For the 6-hour test, three immature rats (wt. 35–45 gm., ages 22–25 days) were each injected subcutaneously with 2 cc. of the night specimen of urine and autopsied at the end of 6 hours.

6-hour ovarian reaction. The ovaries were enlarged and bright red in appearance in sharp contrast to the small, white or faintly pink ovaries of the control animals. Microscopic examination of the ovaries at 6 hours revealed in the majority, perifollicular zones of vaso-dilatation and diffuse hyperemia of the parenchyma of the ovary (fig. 1, 2). Not infrequently, microscopic examination of fixed and stained sections failed to reveal the vaso-dilatation in ovaries which, in situ, were observed to be markedly hyperemic. This discrepancy is in part probably attributable to the formalin and alcohol fixation and in part to disruption of the ovarian capsule, the dilated vessels of which contributed to the grossly visible red appearance of the ovaries.

24-hour test. Two immature albino rats (wt. 35–

Received for publication January 2, 1942.

45 gm.) were given a single subcutaneous injection of 2 cc. of the urine to be tested and the animals autopsied at the end of 24 hours.

24-hour ovarian reaction. Ovaries of animals autopsied 24 hours after the administration of 2 cc. of pregnancy urine showed a characteristic gross reaction of vascular congestion essentially similar to that observed at the end of 6 hours.[1] Serial sections of the 24-hour ovaries revealed varying degrees of perifollicular and hilar vaso-dilatation.

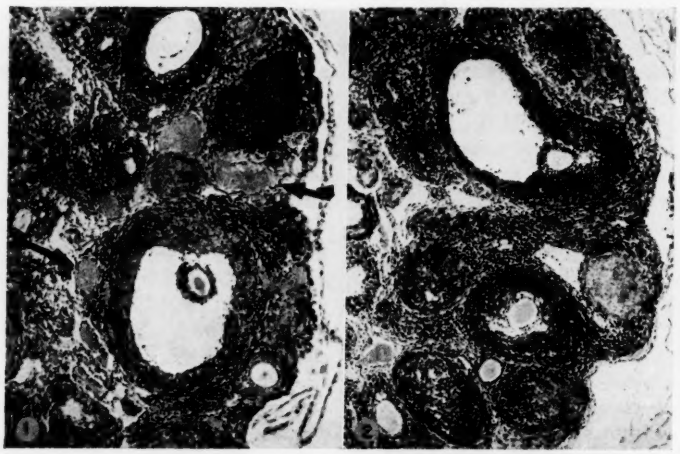

FIG. 1. SECTION OF OVARY OF IMMATURE RAT (wt. 35 gm.) 6 hours after injection of 2 cc. of pregnancy urine, showing perifollicular vascular dilatation. ×70.

FIG. 2. SECTION OF OVARY OF CONTROL RAT 6 hours after injection of 2 cc. of urine from nonpregnant cyclical woman. Note absence of hyperemia. ×70.

24-hour vaginal reaction. The vaginae of animals examined 24 hours after the injection of pregnancy urine were noticeably thicker and broader than those of the controls. Naked eye recognition of the vaginal hypertrophy is easily accomplished as soon as one familiarizes oneself with the difference in gross appearance of the excised vaginae of the positive and control animals. Microscopic examination of sections of the vaginae revealed that the increased thickness of the vagina was due to proliferation of the vaginal epithelium and hypertrophy and edema of the muscularis (fig. 3, 4.)

Tests of Unknown Urines

Results of 6-hour tests. One hundred and ten urine specimens 78 from pregnant women (the length of pregnancy varying from approximately 18 to 280 days), one from a patient with chorioepithelioma and 31 from nonpregnant sources (instances of cyclical menstruation, primary and secondary amenorrhea, menopause, functional sterility with delayed menstrual periods, adrenal cortex carcinoma and normal males) were used. With but one exception, all of the tests performed on the urine from various stages of pregnancy and from the chorio-epithelioma case were read as positive. The one exception was a negative reading made on the urine of a patient 5 days after the date of her expected period. The test was repeated one week later and found to be strongly positive. The subsequent clinical course confirmed the diagnosis of pregnancy. Of 234 animals injected with pregnancy urine, 8 showed borderline reactions. In each instance, however, the mates injected with the same specimen had strongly positive reactions. All of the 31 tests performed on urine from nonpregnant sources (except for the chorio-epithelioma cases) were read as negative.

Results of 24-hour tests. The urine specimens tested consisted of 61 obtained from women in whom pregnancy was subsequently verified clinically, and 57 from nonpregnant women comprising normal cyclical, menopausal, ovariectomized and amenorrheic women. Of the 118 unknowns tested, at the end of 24 hours the gross ovarian and vaginal reactions conformed to the clinical diagnosis in all but two instances. The two exceptions were a false negative ovarian and vaginal reaction obtained in a very early pregnancy

[1] Recently, Frank and Berman (2) have reported similar observations. These authors employed 2 injections of 5 cc. of urine, 6 hours apart, into each of 2 rats weighing 50 grams. For the reading, they recommend examination of the ovary by transmitted light with the aid of a lucite rod, using 10 loupe magnification, 24 hours after the first injection.

(4 days after the expected period) and a false ovarian negative with positive vaginal reaction in a late pregnancy (10 days before term). In the first instance, a repetition of the test, several days later, resulted in a dual positive reaction and, in the second, the ovarian reaction was equivocal in the repeated test and the vaginal reaction remained positive. Microscopic examination of the latter ovaries failed to reveal more than a slight degree of congestion, whereas the vaginae showed striking evidence of estrogenic stimulation in both the epithelial and muscular coats. The negative ovarian reaction is probably attributable to the low concentration of gonadotropin present in this advanced stage of pregnancy, whereas estrogenic hormone was present in sufficiently high concentration to evoke the characteristic vaginal reaction.

DISCUSSION

It appears from this study that the administration of human pregnancy urine to immature female rats results in marked hyperemia of the ovaries which is grossly visible 6 hours after the injection. That this vascular reaction is due to the gonadotropic factor present in pregnancy urine was shown by the production of a similar vascular reaction with chorionic gonadotropin[2] and by the failure to induce the reaction with pregnancy urine, in which the gonadotropin had been inactivated by boiling. This study has revealed, furthermore, that the urine of pregnant women contains estrogens in such high concentration, that administration of 2 cc. of urine to an immature rat causes proliferation of the epithelial and muscular coats of the vagina, which is detectable microscopically and grossly, 24 hours after the injection. The proliferative changes in the vaginal mucosa are identical with those induced by estrogens. It is interesting in this connection, to recall that Allen, Smith and Gardner (3, 4) have reported a proliferative reaction in the vaginal mucosa of ovariectomized adult mice 9½ hours after the administration of estrone and colchicine and suggested this reaction as a test for estrogen. We have found microscopic evidence of epithelial proliferation as early as 6 hours after the administration of pregnancy urine and colchicine but, since these changes could not be detected grossly, they are of no practical value as a test for pregnancy. At 24 hours, however, the vaginal reaction appears to be as reliable an indicator of human pregnancy as the ovarian vascular reaction.

That the vaginal reaction is attributable to the estrogens present in the urine and is not mediated through the ovaries was shown by the induction of epithelial proliferation in the vaginae of immature rats with pregnancy urine in which the gonadotropin had been inactivated by boiling and also by the fact that a similar vaginal reaction was induced with pregnancy urine in immature ovariectomized rats. Neither the ovarian nor the vaginal effects have been produced by comparable amounts of the urine of normal cyclical women or by the gonadotropin-containing urine of ovariectomized women or women with functional amenorrhea or the menopause syndrome.

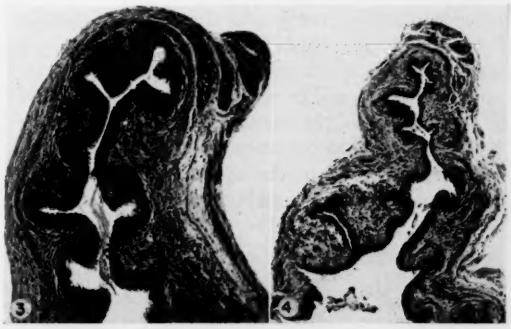

FIG. 3. CROSS SECTION OF PART OF THE VAGINA OF AN IMMATURE RAT (wt. 36 gm.) 24 hours after the injection of 2 cc. of pregnancy urine. Note the marked proliferation of the epithelial cells and increased thickness of the muscularis. ×45.

FIG. 4. CONTROL. CROSS SECTION OF PART OF THE VAGINA OF AN IMMATURE RAT (wt. 35 gm.) 24 hours after the injection of 2 cc. of urine from a normal cyclical woman. ×45.

Although the series of unknowns tested at 6 hours is rather small, the results have been sufficiently consistent to merit recommending it as a simple, rapid and comparatively inexpensive test for human pregnancy. If, for some reason, it is inconvenient to examine the ovaries at 6 hours, the animals may be autopsied at any time during the following 24 hours. Since the end-point of the test consists of hyperemia of the ovaries, it is imperative that the ovaries be examined immediately after death. It has been our practice to asphyxiate the animals with illuminating gas. In performing the autopsy, it is, furthermore, important to avoid injuring vessels in the abdominal wall, since blood in the abdomen makes it difficult to detect the ovarian hyperemia.

The 6-hour test described here has the advantage of being more rapid and less costly than the Ashheim-Zondek test which is performed on 5 mice and takes 96 hours, and the Friedman test which gives the most accurate results when performed on 2 rabbits and requires 48 hours (5).

We have found it most convenient to inject the animals at 10 A.M. and perform the autopsies at 4 P.M. It is important for those planning to use this

[2] The chorionic gonadotropin (Pranturon) was a product of Schering Corporation, Bloomfield, New Jersey.

test to become familiar with the normal gross appearance of the ovaries of immature rats. It is advisable to start with a series of known pregnancy urine specimens and to contrast these ovarian reactions with those induced by negative urines before attempting to obtain readings of unknowns for diagnostic purposes.

SUMMARY AND CONCLUSIONS

A 6-hour test for human pregnancy is described, based on the observation that the chorionic gonadotropin causes a marked hyperemia of the ovaries of immature rats, which is grossly discernible 6 hours after the injection. For the performance of this test it is recommended that three animals (wt. 35–45 gm.) be each injected with 2 cc. of the first morning specimen and autopsied at the end of 6 hours. Positive results were obtained in all but one of 78 tests of pregnancy urines and negative results in all of the 31 tests of urine specimens from nonpregnant individuals.

A confirmatory 24-hour test is also described which is based on the proliferation of the epithelial and muscular elements of the immature rat vagina induced by the estrogens present in the pregnancy urine. Confirmation by the 24-hour vaginal reaction is unnecessary as soon as one becomes familiar with the 6-hour ovarian vascular reaction.

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On the Mechanism of Insulin Resistance in Toxemic States[1]

[Carbohydrate Metabolism]

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IT IS WELL known that the early stages of toxemia, from whatever cause, may be accompanied by hyperglycemia, glycosuria, and a diminished carbohydrate tolerance as indicated by the dextrose tolerance test (1, 2). The response to a given dose of insulin is less than that in the normal individual (3). Diabetic patients who were formerly well controlled by a small dose of insulin may, with the advent of toxemia, be poorly controlled even with very large insulin dosages (4). This condition has been commonly referred to as 'insulin resistance.'

Previous work has clearly shown that the liver is a major factor in determining carbohydrate tolerance (5). It has also been demonstrated that liver damage by toxins diminishes carbohydrate tolerance by interfering with the homeostatic mechanism for the maintenance of the constant normal blood sugar level (6, 7). Since insulin is an important regulator of this heptatic mechanism, it was logical to seek the cause of insulin resistance in the liver.

Our knowledge of the chemical steps involved in the buildup and breakdown of liver glycogen has undergone a radical change within recent years. It was formerly thought that hepatic glycogenolysis normally occurred through amylase activity, the glycogen being degraded through dextrins to maltose and to glucose (fig. 1). However, Lee and Richter (8) who recently summarized the previous work on liver amylase and reported there own thorough studies on the subject, pointed out that *a*), even the highest amylase activity found in the blood, liver and other organs is only of the order of 1/10,000 of the amylase activity of the pancreas; *b*), the small amounts of amylase found in the liver and other organs may be regarded as traces of the very active pancreatic and salivary amylases which have diffused into the blood and throughout the system; and *c*), the amylase present in the liver probably exerts little or no activity *in vivo*, because of the absence of a sufficient concentration of free chloride ions within the hepatic cells. They concluded that the amylase found in the liver is not concerned in any normal hyperglycemic mechanism. More recently Somogyi (9) has analyzed the carbohydrates present in normal liver and has found only glycogen and dextrose, with no trace of maltose or other nonfermentable reducing substance such as would result from amylase activity. Since he has never been able, by any method to extract more amylase from the liver than would correspond to the enzyme

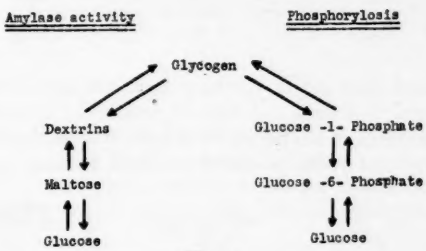

Fig. 1.

content of the extracellular fluid, Somogyi has concluded that the hepatic cells contain no amylase whatever.

On the other hand, the work of Parnas (10), Cori (11, 12) and Ostern and Holmes (13) has been generally recognized as demonstrating that the steps between glycogen and glucose in the liver are mediated by phosphorylating mechanisms (fig. 1). It has been shown that the rates of these transformations are sufficiently rapid to account for even the most intense forms of hyperglycemia encountered *in vivo*. It is presumably upon these or related phosphorylations that insulin exerts its regulatory influence (14), although its exact point of action is still unknown.

Whether or not some small amount of inactive amylase is normally present within the hepatic cells, it occurred to us that in the liver damaged by toxins the normal barrier which excludes amylase or the normal environment which inhibits amylase activity might be disturbed. In either case liver glycogen would then be broken down through this abnormal

Received for publication January 17, 1942.
[1] Aided by the A. B. Kuppenheimer Fund.

pathway, as well as by phosphorylosis. Since only the normal portion of the combined glycogenolysis would be subject to control by insulin, this could account for the socalled insulin resistance. The experimental data to be presented supports this hypothesis.

METHODS

The study of the hepatic enzyme activities before and after the influence of toxin necessitated the repeated sampling of the liver from the same living animal; this work was done on dogs under nembutal anesthesia. It was necessary to quickly wash the liver samples as free as possible from blood, because of the probability that the altered membrane permeability of the excised liver cells would soon allow the relatively large amounts of blood amylase to enter. In preliminary experiments it was found that when the liver was washed *in vivo*, (with cold tap water, through a large needle inserted into the distally occluded portal vein) and immediately removed, it was substantially free from blood and blood amylase, as judged by the negligible rate of glycogenolysis in a phosphate-free medium. This procedure, however, was not suitable for our work since we wished to compare the enzyme activity of samples of the same liver before and after the influence of toxin. We were fortunately able to accomplish the same result by removing small samples of tissue from the intact organ and immediately washing them under a strong current of cold tap water. Although the latter procedure might conceivably wash out some of the small amount of amylase which may be present in the liver cells both the control samples and those obtained after treatment with toxin were treated in the same manner, and the results should be comparable. All of the determinations of enzyme activity referred to below were therefore made on liver samples which had been washed free from blood amylase in this way.

TABLE 1. INFLUENCE OF DIPHTHERIA TOXIN ON LIVER GLYCOGEN IN VIVO

Glycogen before injection	Time after toxin injection	Glycogen after injection
gm. %	*hr.*	*gm. %*
6.46	3.5	1.85
5.47	3.5	1.41
5.25	4.0	1.28
5.14	3.0	2.63
4.28	2.5	1.38
3.53	3.5	1.07
3.40	3.5	0.37
3.31	3.0	0.90
3.10	3.5	0.30
2.16	2.0	1.19
1.98	3.0	0.39
0.60	3.0	0.07
0.59	2.5	0.31

The general experimental procedure was as follows. A laparotomy was performed on the anesthetized normal animal and a sample of liver was excised for control determinations. One portion of the sample was immediately frozen in carbon dioxide ice and used for the determination of the initial values of total carbohydrates, glycogen, free sugar, organic and inorganic phosphates. Another portion was washed, minced and used for the determination of glycogenolytic activity. Meanwhile the animal's abdomen had been closed and 100 to 180 M.L.D. of diphtheria toxin[2] per kg. of body weight had been injected intravenously. Two to 4 hours later addi-

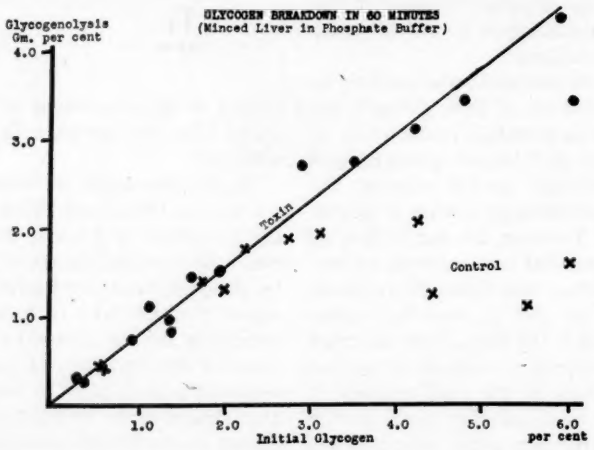

Fig. 2

[2] We are indebted to Eli Lilly & Company of Indianapolis, Indiana, for a supply of standardized potent diphtheria toxin.

tional samples of the liver were taken and the above determinations repeated. The type and amount of toxin used had been shown to effect carbohydrate tolerance significantly within the specified period in previous experiments under comparable conditions (6, 7).

The total carbohydrates were determined by the method of Benoy and Elliot (15). The free reducing substances, referred to as 'free sugar' for the sake of brevity, were estimated by the same method, omitting hydrolysis in acid. The glycogen was determined by the method of Good, Kramer and Somogyi (16). The analysis for inorganic phosphate was made by the procedure of Fiske and Subbarow (17); the hexose phosphate content was calculated from the P value after hydrolysis for 100 minutes in HCl[3] (18, 19).

RESULTS

Table 1 summarizes the data on the initial glycogen content of liver samples removed before and after the

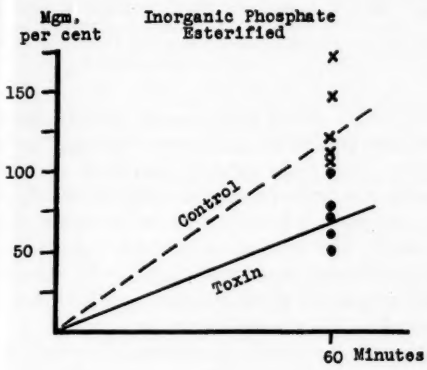

Fig. 3

administration of toxin. It is evident that the amount of toxin used and the time intervals resulted in a marked loss of glycogen *in vivo*, regardless of the control level.

The loss of liver glycogen *in vivo* could have been due to an increased rate of glycogenolysis, a decreased rate of glycogenesis, or both. That increased glycogenolysis was an important factor was shown by the results of the experiments *in vitro* which are summarized in figure 2. Finely minced liver was suspended in Hasting's Ringer Phosphate and incubated at 38° C. The samples of normal liver exhibited rates of glycogenolysis proportional to their initial glycogen levels, when the latter were low. However, above levels of 2.0 to 2.5 per cent initial glycogen which is within the usual normal range, the rate of glycogenolysis no longer increased with the initial glycogen level, but remained more or less stationary at a rate of 2.0 gm. per cent per hour or less. In sharp contrast to this, the samples of liver removed after toxin administration showed rates of glycogenolysis proportional to the

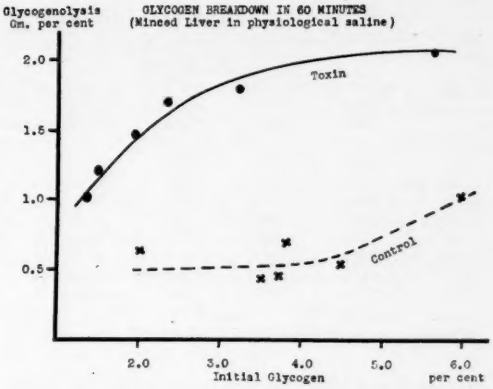

Fig. 4

initial glycogen level at all values of the latter. Thus at initial liver glycogen levels of 5.0 to 6.0 per cent,[4] the rate of glycogenolysis was more than twice as rapid in the samples of toxic liver as in those of the normal.

An indication of the pathway through which the excessive glycogenolysis induced by toxin occurred was gained by observing the disappearance of inorganic phosphate when the minced liver was incubated in phosphate buffer (M/15) at pH 7.4. Sodium fluoride (0.2 per cent) was added to inhibit dephosphorylation (20). Figure 3 shows that the rate of phosphorylation in toxic liver was only about half that in normal liver. It was evident that the more rapid breakdown of glycogen caused by toxin must proceed by a pathway other than phosphorylosis. However, since the formation of glycogen is also by phosphorylosis, the diminution of this process might partly account for low initial liver glycogen values in toxic liver on the basis of interference with glycogenesis.

[3] The phosphate attached to hexoses was calculated according to the formula

$$P_{hexose} = (P_{100} - P_7)5/4$$

P_{100} = phosphate appearing after 100 min. hydrolysis.
P_7 = phosphate appearing after 7 min. hydrolysis (mainly adenosine triphosphate)

[4] In order to be able to compare normal and toxic liver samples at equivalent glycogen levels in this range, it was necessary to add glycogen to some of the minced preparations of the latter samples. The finding that the rate of glycogenolysis depended partly upon the initial glycogen level made it essential to obtain other data in relation to initial glycogen levels. Additions of glycogen to liver mince were therefore made whenever necessary for comparative purposes.

If the abnormal pathway for increased glycogenolysis were due to amylase activity, one would expect it to occur in the absence of phosphate in the medium, providing sufficient chloride ions were present for its activation. Figure 4 shows that this prediction was fulfilled. When incubated in a medium of 0.85 per cent NaCl, specimens of minced toxic liver still exhibited an excessive rate of glycogenolysis as compared to normal liver. The unavoidable presence of about 6 mg. per cent of phosphate derived from the liver itself was sufficient to account for the slow rate of glycogenolysis observed in the normal liver under these conditions.

Finally, the abnormal activity of amylase in toxic liver was confirmed by the demonstration of the presence of one of its characteristic endproducts, which is not found in normal liver. Table 2 summarizes the data on carbohydrate partitions made on liver samples removed before and after toxin administration, and immediately frozen in carbon dioxide ice to prevent any autolytic change. With two exceptions, the control liver samples contained no other carbohydrate than glycogen, free sugar and hexose phosphates. In tissue from *dog 26*, the amount of other carbohydrate was hardly significant. *Dog 23* was interesting in that its liver, which did contain a significant amount of other carbohydrate, was obviously not normal. After toxin administration, all of the specimens of liver contained significant amounts of the abnormal carbohydrate. This moiety was not precipitable by alcohol, yielded free sugar on acid hydrolysis, and was probably a mixture of dextrins.

Table 2. Occurrence of polysaccharides in liver damage

No.	Before Toxin					After Toxin				
	Total CHO	Glycogen	Free sugar	Hexose-phosph.	Poly-sacchar.	Total CHO	Glycogen	Free sugar	Hexose-phosph.	Poly-sacchar.
19	2433	2155	247	33.3	±0	1758	1185	312	39.9	221
20	5486	5142	392	53.6	±0	3614	2634	293	63.6	629
21	5624	5252	302	60.5	±0	1724	1284	256	62.9	122
22	3554	3308	170	73.8	±0	1320	895	200	84.9	140
23[1]	1002	610	123	49.4	220	321	71	53	47.0	150
24	6585	6457	129	37.6	±0	2337	1853	245	33.6	186
25	3712	3396	344	54.3	±0	970	369	158	74.9	368
26	3784	3530	143	48.7	62	1575	1070	193	55.7	256

[1] Marked distemper, fatty liver. All values in mg. %

SUMMARY AND DISCUSSION

Carbohydrate partitions and determinations *in vitro* of enzyme activity were made on samples of liver removed from nembutalized dogs before and after the administration of suitable amounts of diphtheria toxin. The samples obtained after toxin administration revealed an increased rate of glycogenolysis despite a diminished phosphorylosis. This indicates a limitation of the normal mechanism for hepatic glycogenesis and glycogenolysis with the appearance of an abnormal pathway for glycogenolysis. The facts that the excessive glycogenolysis in toxic liver was also demonstrated in a phosphate-poor medium, and that it gave rise to characteristic endproducts not found in normal liver, point to amylase activity as the abnormal process unleashed by the toxin.

Insulin exerts a regulatory influence, direct or indirect, on the normal mechanism of glycogenolysis by phosphorylosis. It is not known to influence amylase activity. Hence the relative impotence of insulin (insulin resistance) in toxemic states, in which amylase activity has become a factor in hepatic glycogenolysis. This situation is probably aggravated by the interference with phosphorylosis by the toxin. That proportion of the glycogenolysis which is still proceeding by phosphorylosis may not be as responsive as it normally is to hormonal control. Also, glycogen synthesis is undoubtedly interfered with (21). Thus it is not difficult to account for the characteristically low level of liver glycogen, the 'diabetic type' of dextrose tolerance curve and the occasional hyperglycemia and glycosuria found in the initial stages of toxic liver damage. In cases of advanced liver damage, when interference with glycogen synthesis and with blood sugar formation has become extreme, hypoglycemia may result (6). In diabetes mellitus complicated by toxemia the above effects are first seen as an increased requirement for insulin, or as a lack of control by even extremely large doses. But severe liver damage may cause an apparent improvement in the diabetes, as the general clinical condition of the patient deteriorates (22).

These results also supplement the rationale for high carbohydrate therapy in liver disease (23) and for high carbohydrate therapy plus insulin in diabetes complicated by liver damage (24). It has been demonstrated previously that the addition of dextrose to

normal minced liver *in vitro* reduces the rate of appearance of free sugar from the liver itself (25) and previously administered insulin reinforces the antiglycogenolytic effect of a given amount of added dextrose (26). The present results may indicate that in the liver damaged by toxin the therapeutically increased supply of blood sugar also helps to push the glycogen-glucose equilibrium in the direction of glycogen by simple mass action on the amylolytic enzymes.

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Arteriosclerosis and Hypothyroidism: Observations on Their Possible Interrelationship

[Thyroid and Arteriosclerosis]

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IT IS WELL recognized that after the age of 40 years the basal heat production tends to decrease (1, 2, 3). DuBois (4) studied the metabolism of an individual from the age of 31 to 54 years and presented excellent evidence of a decline in the basal metabolic rate with advancing age. Generally, the decrease in metabolism has been ascribed to involutionary changes which take place in the thyroid gland; undoubtedly, other factors play a part but these will be discussed later. It appears plausible that the advent of arteriosclerosis may be correlated at times with decreased activity of the thyroid gland. At least, some observations have been carried out on animals which would lend support to such a hypothesis.

In 1913, Anitschkow (5) and Wacker and Hueck (6) demonstrated that the aorta of rabbits fed diets high in cholesterol frequently became atherosclerotic. Since then, this observation has often been confirmed and the degree of atherosclerosis thus produced in general was found to parallel the elevation in blood cholesterol. Moreover, there appears to be some relationship between hypercholesterolemia and this vascular lesion in man since atherosclerosis is not uncommon in such diseases as diabetes, nephrosis, myxedema, lipoid granulomatosis and hypercholesterolemic xanthomatosis. When rabbits were fed potassium iodide, thyroxin or thyroid substance simultaneously with cholesterol, atherosclerosis of the aorta was inhibited (7–13). This observation indicates that in the experimental animal at least, some antagonism exists between the thyroid gland and the susceptibility of the vascular tree to lipoid infiltration.

In the present study, the possible relationship between arteriosclerosis and the activity of the thyroid gland was applied to the human problem. Investigations were carried out on subjects 55 years or older and in each instance, the basal metabolic rate was correlated with the presence or absence of arteriosclerosis according to the clinical criteria described below.

MATERIAL AND METHODS

The records of 24,000 basal metabolic rate determinations[2] were reviewed. The studies were made on both ambulatory and hospitalized patients at the Respiration Laboratory of the New York Post-Graduate Hospital from Jan. 1, 1930, to July 1, 1940.

The gasometer method as modified by Bailey (14) was the method used. Carbon dioxide and oxygen were determined in expired air by the Haldane (15) method as modified by Henderson (16) and Bailey (14). Each step was checked from the calculation sheets outlined by Boothby and Sandiford (17). The basal metabolic rate was compared with Aub-DuBois Standard as modified by Bailey (18). These standards are almost identical with those published by Berkson and Boothby in 1936 (19) and give most accurate results for all types of cases (20–23). For the actual procedure, most of the accepted methods were followed. The subject was tested before breakfast after a 12 to 15-hour fast. The various factors influencing the basal metabolic rate such as age, sex, height, weight, pulse, temperature and respiratory rate were recorded. The patient was put at rest on a comfortable cot located in a room furnished to resemble any home sittingroom. The gasometers and the apparatus used for gas analyses were kept in an adjoining room so as not to overwhelm the patient. With the patient at rest, his confidence and coöperation were quietly secured. The mask was a French type, used in conjunction with a rubber flutter valve introduced by the British in the first World War, as adopted by Bailey (14, 24). It was firmly applied over

Received for publication December 29, 1941.

[1] Oliver Rea Research Assistant in Medicine.

[2] With permission of Dr. Cameron V. Bailey.

the entire face of the subject. This type of mask caused no discomfort or increased respiratory rate such as might be induced by a mouth-piece and nose-clip to sensitive patients. These modifications helped to allay fear and allowed for complete body rest.

From the 24,000 records obtained by the above method, 755 were of patients 55 years or older. However, only 293 records were accepted for analysis. The remainder were discarded because of incomplete data, cardiac decompensation, thyroid disorders, blood dyscrasias, history of previous thyroidectomy or treatment with iodides, thyroid extract or roentgen ray. The present study, therefore, was confined to 293 subjects who were 55 years or older, and in whom no metabolic disorders or other factors were present which might abnormally influence the basal metabolic rate.

The clinical records of the subjects thus chosen were then reviewed with a view to determining the presence or absence of arteriosclerosis. The clinical criteria used were: *a*), peripheral vascular thickening, tortuosity, beading or absent pulsation; *b*), intermittent claudication; *c*), vascular changes in the ocular fundi; *d*), roentgen-ray evidence of peripheral arteriosclerosis and of widening or thickening of the aorta

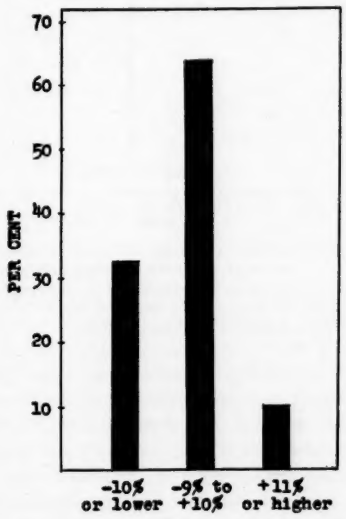

FIG. 1. FREQUENCY DISTRIBUTION OF BASAL METABOLISM IN 293 SUBJECTS OVER THE AGE OF 55 YEARS.

or its arch; *e*) wide pulse pressure; and *f*) urine analysis indicative of nephrosclerosis.

No attempt was made to grade the degree of arteriosclerosis. If any subject satisfied at least two of the criteria outlined above, arteriosclerosis was considered to be present and, as will be seen later, this crude procedure proved, nevertheless, to be fairly accurate.

RESULTS

Figure 1 indicates the frequency distribution of the basal metabolic rate for the total group of 293 patients. Of these, 27 per cent had a B.M.R. of 10 per cent or more below the average normal, 64 per cent

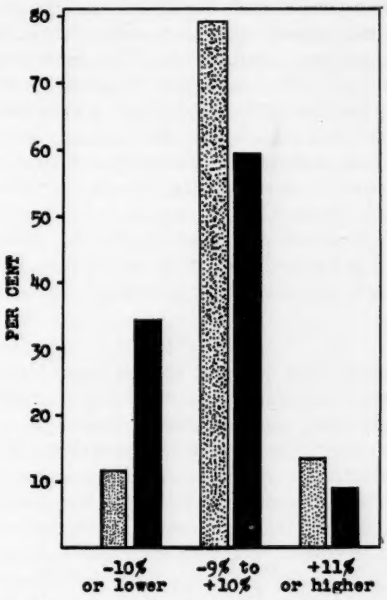

FIG. 2. FREQUENCY DISTRIBUTION OF BASAL METABOLISM IN 223 SUBJECTS WITH ARTERIOSCLEROSIS (SOLID RECTANGLES) AND IN 70 SUBJECTS WITHOUT ARTERIOSCLEROSIS (SHADED RECTANGLES) OVER THE AGE OF 55 YEARS.

were between 10 per cent below and 10 per cent above the average normal, and 9 per cent were 11 per cent or more above the average normal. There is, therefore, a tendency for the basal metabolic rates of patients over the age of 55 years to shift to the low side of normal as compared with observations made by Boothby and Sandiford for all age groups (2, 21). The latter workers found that 92 per cent of normal individuals have a basal metabolic rate within 10 per cent below and 10 per cent above the average normal.

Figure 2 shows that the incidence of hypometabolism (10% or more below the average normal) in non-arteriosclerotic subjects is only 10 per cent as compared with an incidence of 32 per cent in persons with arteriosclerosis. Furthermore, the distribution of basal metabolism values in non-arteriosclerotic subjects is quite similar to what may be expected in the average population, namely, 77 per cent exhibiting a basal metabolism between 10 per cent below and 10 per cent above the average normal and the re-

mainder equally distributed at the extremes. It may be stated, therefore, that the general metabolic trend downward in persons 55 years and older may be ascribed to the greater incidence of a lowered basal metabolic rate in those manifesting arteriosclerosis.

In figure 3, the individual basal metabolic rates of the 293 subjects are plotted against age. Since 76 per cent of the individuals studied showed some evidence of arteriosclerosis, two disproportionate groups are segregated, namely, 223 subjects with arteriosclerosis and 70 without arteriosclerosis. This figure demonstrates that between the ages of 55 and 65 years, the average basal metabolic rate for both groups tends to rise slowly and then declines after the age of 65 years. A pronounced decrease in the average basal metabolic rate occurs in arteriosclerotic patients 70 years or over, but comparable figures could not be obtained in the non-arteriosclerotic subjects since no person in this age group could be classed as free from arteriosclerosis by the criteria already outlined.

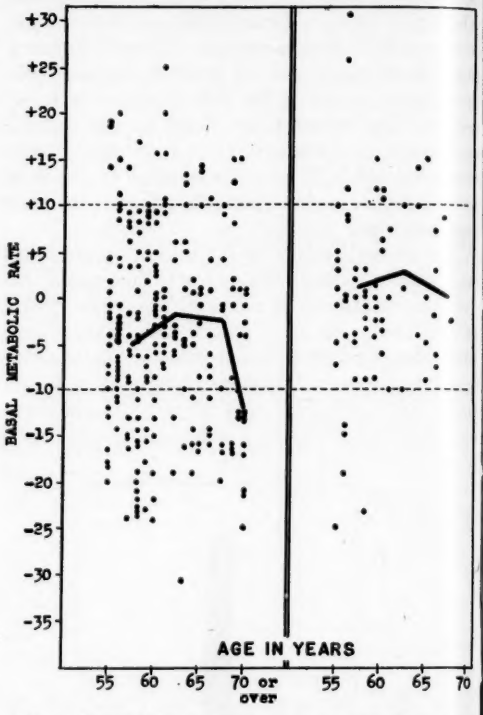

FIG. 3. CORRELATION OF INDIVIDUAL BASAL METABOLIC RATES WITH AGE IN 223 SUBJECTS with arteriosclerosis (left segment) and in 70 subjects without arteriosclerosis (right segment) over the age of 55 years. The average basal metabolic rate in 5-year periods for each group is indicated by the solid lines.

DISCUSSION

As mentioned before, it appears justifiable to assume that a hypofunctioning thyroid gland may be a factor in aiding the deposition of cholesterol in the vascular tree. Leary (25), too, intimates that decreased thyroid activity may hasten the atherosclerotic process. It should not be overlooked, however, that arterial disease may be primary and that atherosclerosis of the arteries supplying the thyroid gland may result in a diminution in the functional capacity of the thyroid gland. There is, perhaps, somewhat more evidence in support of the first assumption although, of necessity, most of it is derived from experiments on animals.

Much controversy has existed over the rôle cholesterol plays in the pathogenesis of arteriosclerosis.[1] Leary (25), particularly, has maintained that hypercholesterolemia will hasten the arteriosclerotic process in human beings, and has championed the thesis that the experimental atherosclerotic plaque commonly seen in the aorta of cholesterol-fed rabbits is the counterpart of the lesion seen in human tissue. Grotel et al. (26) concluded, after a study of human pathologic material, that a definite relationship existed between excessive intake of cholesterol and the development of arteriosclerosis. Davis, Stern and Lesnick (27) reported higher cholesterol levels in the blood of patients with angina pectoris of arteriosclerotic origin than in normal subjects. Poindexter and Bruger (28) presented evidence of a significant increase in the plasma cholesterol in patients with hypertensive and arteriosclerotic heart disease. On the other hand, Duff (29) argued that the atherosclerotic lesion produced in rabbits by the feeding of cholesterol is not identical with that of human arteriosclerosis. Weiss and Minot (30) and Watson and Wharton (31) stated that a high cholesterol diet alone is not the chief factor in the development of the arteriosclerosis in humans. Page, Kirk and VanSlyke (32), maintained that arteriosclerotic changes in patients with hypertension were not caused by hyperlipemia, hypercholesterolemia, or by an elevation in cholesterol: phosphatide ratio. Landé and Sperry (33) likewise maintained that there was no relationship between the degree of atherosclerosis and the level of serum cholesterol. Page (34) concluded that hyperlipemia was not essential for the development of atherosclerosis. Elliot and Nuzum (35) reported that patients with essential hypertension, with or without arteriosclerosis, did not have an elevation in blood cholesterol.

As indicated previously, the consensus of opinion has been that in diabetes, in which elevated blood cholesterols are not infrequently encountered, atherosclerosis develops more rapidly (36–42). Yet this, too, is by no means settled. Hunt has shown (43) that the

most advanced arteriosclerosis may be found in patients with comparatively low levels of plasma cholesterol. Warren (44), however, believed that the feeding of diets high in fat and rich in cholesterol to diabetics in the decade between 1920 and 1930 increased the incidence of arteriosclerosis.

The basal metabolic rate was used here as an index of thyroid activity. Of course, it may be questioned whether a decrease in basal metabolic rate in older persons actually indicates a hypofunctioning thyroid gland. Lorand (45) is in favor of this view. On the other hand, it might be argued that in senescence, persons tend to ingest less food, thereby causing lowered heat production. It has been shown, however, that with diminished food intake or omission of various dietary factors, thyroid structure as well as function might be modified or impaired (46–49). Whatever the cause, dietary or otherwise, the end result is diminished thyroid activity.

It is conceivable that other endocrine glands may in some way influence the arteriosclerotic process. Yet, gonadotropic hormones (testosterone propionate and estradiol dipropionate) have not been found to inhibit atherosclerosis in rabbits as consistently as do thyroid extracts, thyroxin or iodine. Ludden, Bruger and Wright (50) have shown that these steroid hormones do not inhibit cholesterol-induced atherosclerosis in male rabbits but they do exert this effect in female rabbits. Bruger and Fitz (51) have shown that the pituitary gland, more specifically the thyrotropic factor of the anterior lobe, does not prevent the deposition of cholesterol in the aorta. On the contrary, if thyrotropic factor of the anterior pituitary and cholesterol are administered simultaneously to rabbits over a relatively long period of time, there appears to be an increased deposition of cholesterol in the aorta.

Postmortem studies by Cooper (52), McCarrison (53), and by Dogliotti and Nizzi Nuti (54) demonstrated that, in older persons, the thyroid gland is reduced in size, the follicles and cells are smaller, the amount of connective tissue is increased and the colloid in the vesicles may be less dense or absent. It would appear, therefore, that the diminished function of the thyroid gland in older persons may be ascribed to these histologic changes. Carlson (55) questions this assumption since he believes there may be very large factors of safety in the thyroid gland.

Wilder (36) feels that the presence of arteriosclerosis cannot with certainty be determined by an examination of living persons. It is also conceded that in very old persons there may be no manifestations of arteriosclerosis, and again Ophüls (56) has shown that arteriosclerosis may be present in comparatively young individuals. Despite these objections, on re-examination of our data, it is noted that even by the crude criteria outlined above, our method of classifying arteriosclerosis seems to be fairly accurate. Without age being used in the diagnostic criteria, it is found that those who were classed as non-arteriosclerotic were not older than 68 years of age. This is what may be expected, since by far the largest number of subjects manifesting arteriosclerotic changes were over the age of 68.

We are in agreement with those who feel that no single factor explains the etiology of arteriosclerosis in human beings; on the contrary, the problem of its pathogenesis is a complex one. The observations referred to earlier in this paper showed the influence the thyroid gland exerts on the production of experimental atherosclerosis, although it should not be implied that only those substances affecting the activity of the thyroid gland modify the degree of atherosclerosis experimentally induced by feeding cholesterol. Malisoff (57), Strauss (58), Thiersch (59), Eberhard (60) and Huber et al. (61) have shown that the administration of potassium thiocyanate, colloidal silicic acid, garlic oil, alcohol and lipocaic, respectively, may inhibit experimental atherosclerosis. Page (34) is led to the concept that a tissue (vascular) susceptibility factor to the imbibition of lipids must exist in order to explain the fact that whereas atherosclerosis of the aorta may be inhibited by feeding iodine to cholesterol-fed rabbits, the degree of hypercholesterolemia remains unaffected. It is conceivable, though of course far from proven, that the receptivity of the vascular tree to the deposition of lipids may vary inversely with the activity of the thyroid gland.

CONCLUSIONS

The incidence of hypometabolism in subjects 55 years or older is greater for those exhibiting arteriosclerosis than for those without arteriosclerotic manifestations. Some theoretical considerations correlating the activity of the thyroid gland and the aging process are discussed.

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Effect of Male Hormone Therapy on Urinary Gonadotropins in Man[1]

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A NUMBER OF INVESTIGATORS have reported on the urinary excretion of gonadotropins following treatment of women with the steroid sex hormones. With the use of either estrogens (1–4) or androgens (3, 5, 6, 7) the increased gonadotropic output of ovariectomized or menopausal women can be abolished, although with small doses of estrogens there may be no material reduction in the titers (8).

Few studies relate to gonadotropin excretion in castrate males treated with the male sex hormones. Frank and Salmon (9) using rather limited doses of androsterone, dihydroandrosterone benzoate, and testosterone reported only slight amelioration of castration symptoms, and no influence on the excretion of gonadotropins. In a preliminary note (10) the present authors reported a definite decrease in the elimination of gonadotropins following administration of testosterone propionate to castrate males. These results are amplified in this paper.

METHODS AND SUBJECTS

Urine specimens for 24 consecutive hours were collected, preserved under refrigeration with 3 cc. of toluene per liter, and shipped within 24 hours to the laboratory. Gonadotropic hormone was extracted by the method of Freed and Hechter (11). Bioassays were performed using 21 to 23-day-old mice from our own stock. They were injected in groups of 3 to 5 animals at dosage levels that were inferred roughly from previous trials. The animals received 6 injections spaced over 36 to 40 hours and were killed at 72 hours. We have employed, with some modification, the technic of Levin and Tyndale (12) which utilizes the uterine weight response as the criterion of gonadotropic activity. We define a mouse unit as that amount of hormone which under standardized conditions causes an increase of 100 per cent in the ratio of uterine weight/body weight. All unitages are expressed in mouse units (M.U.) per 24 hours. The response to 0.1 international unit of equine gonado-

TABLE 1. CLINICAL AND ENDOCRINE DATA ON GROUP OF SUBJECTS STUDIED

Case No. and Status	Age	Ht.	Wt.	Urinary excretion prior to treatment or after cessation of therapy for several weeks		
				Gonadotropins	Androgens	Estrogens
	yr.	cm.	kg.	M.U.	I.U.	I.U.
11. Castrate for 20 yr.	43	172.5	66.8	30–140	8	28
12. Castrate for 26 yr.	45	156	69.0	50–70	3	11
13. Castrate for 13 yr.	56	180	72.0	30–80	9	5
14. Castrate for 13 yr.	39	162.5	73.6	10–40	11	15
15. Castration phenomena since attempted repair of bilateral hernia 2 yr. before	43	170	81.8	30	23	25 35
16. Unilateral cryptorchid till 35th yr. when descended testis was removed surgically with immediate, severe and sustained castration phenomena	35	177	70.5	40–240	13.5	8

Received for publication January 16, 1942.

[1] This study has been supported in part by grants from the International Cancer Research Foundation, the Rockefeller Foundation, and the Fluid Research Fund of Yale University School of Medicine.

tropin approximates one such M.U. (Catchpole, unpublished data).

The present study concerns 4 castrate male subjects and 2 men who developed primary gonadal insufficiency following attempted repair of indirect inguinal hernias (table 1). Three of these men were studied over a period of more than two years. The plan of the experiment involved successive periods in which therapy with androgenic hormones was alternately given and withheld.

Several methods of administration of the hormones were tried. Testosterone propionate[2] was injected intramuscularly in peanut oil solution or implanted subcutaneously in the form of pellets. Tablets of methyl testosterone[2] were given by mouth. Gonadotropic assays were made on the urines of these patients at frequent intervals before, during and after courses of hormone administration. In order to guard against failure to detect small amounts of hormone occurring either normally or as a result of medication we have always attempted to obtain 2 or more urine specimens on consecutive days. The patients kept daily records of certain subjective changes such as the number and nature of hot flushes, sweating and penile erections.

[2] Testosterone propionate (Perandren) and methyl testosterone (Metandren) were supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

RESULTS

Table 1 summarizes the clinical data together with those of the gonadotropic and sex hormone assays performed either prior to the present course of treatment, or during periods of nontreatment. The data on sex hormone output were obtained in collaboration with Dr. R. I. Dorfman, and are reported elsewhere (13). Values for the urinary hormone excretions are given for *subjects* 13 and 15 to supplement the scanty data available for such in castrate men; these individuals were not studied with respect to gonadotropic excretion following androgenic therapy.

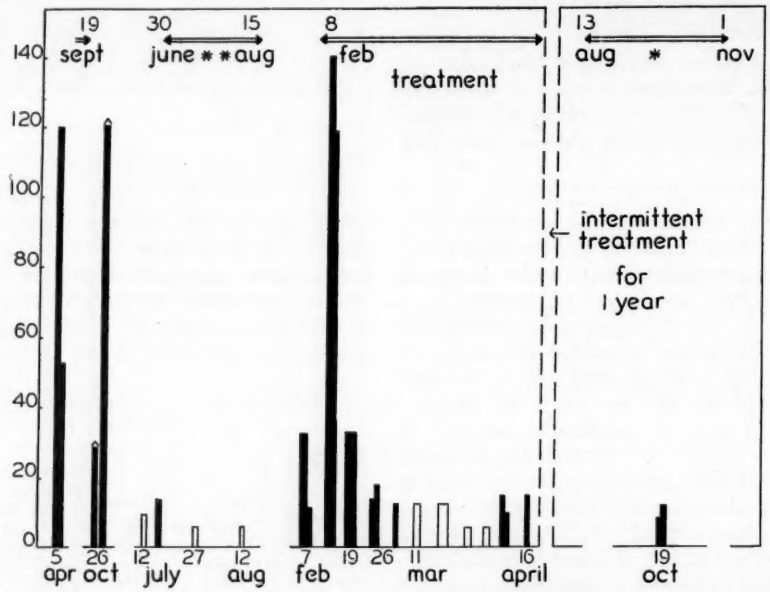

Fig. 1. Excretion of gonadotropic hormone in *case 11* during periods of nontreatment, and treatment with androgens. The androgens used were testosterone propionate given intramuscularly, pellets of testosterone propionate implanted subcutaneously (**), and methyl testosterone given orally (*).

In figures 1 to 4, clear columns indicate that assays for gonadotropin were negative at the level tested. The sign $\wedge$ indicates amounts greater than tested levels.

Considerable variation was found in the daily excretion of gonadotropic hormone not only between different subjects but also in the same subject.

CASE REPORTS

Case 11 (fig. 1). Preliminary assays showed an excretion of 50 to 120 M.U. of gonadotropins in April, 1938. Daily intramuscular injections of 20 mg. of testosterone propionate in oil were given from July 11th to Sept. 19th. By Oct. 26th all effects of this treatment had subsided, two determinations showing greater than 30 M.U., and 120 M.U. of gonadotropins respectively. This indicated that the titer had not changed appreciably from that observed prior

to medication. On June 30th of the following year an amount of 280 mg. of testosterone propionate was implanted subcutaneously as pellets. By July 12th tests showed that urinary gonatropins had diminished to an equivocally positive value of 10 M.U. On July 17th the assay values were 14 M.U. and subsequent tests during the months of July and August were negative. After extrusion of many of the pellets in the middle of August the patient did not again receive therapy until Nov. 21st when 20 mg. of testosterone propionate daily was given intramuscularly in oil until Dec. 27th of that year. After more than a month without treatment, daily injections of 20 mg. of testosterone propionate were resumed on Feb. 8, 1940. Two preliminary assays showed 25 and 10 M.U. of gonadotropins on successive days. The reason for these low values is unexplained, since assays performed 5 and 6 days after initiation of treatment showed 120 and 140 M.U. respectively. With continued androgenic treatment

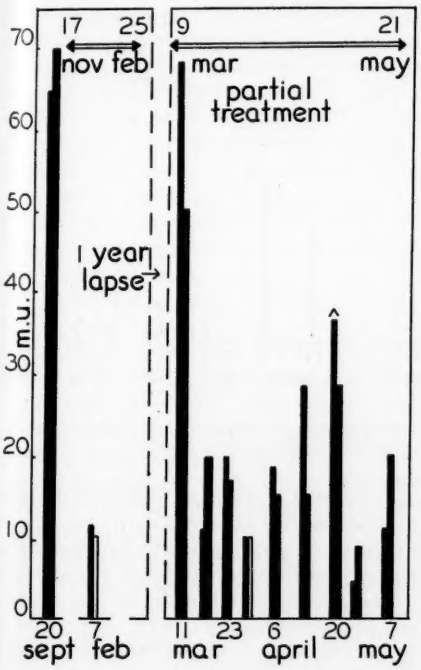

Fig. 2. EXCRETION OF GONADOTROPIC HORMONE IN *case 12* during periods of non-treatment and treatment with testosterone propionate intramuscularly.

the patient excreted diminished quantities of gonadotropins and after March 11th the findings were usually negative for tests of 6 to 10 M.U. It was interesting to note that during the course of treatment small 'escape' amounts of gonadotropic hormone were occasionally found. After the lapse of a year during which treatment was given intermittently, a further course of therapy was begun on Aug. 13, 1941. The subject received 35 mg. of methyl testosterone daily by mouth, this dose being increased to 70 mg. per day on August 20th for effective clinical control. Two months later, assays performed on October 19th and 20th were positive for 6 and 12 M.U. of gonadotropin per 24 hours respectively, showing that pituitary suppression had been obtained.

Case 12 (*fig. 2*). Initial titers of 65 to 70 M.U. of gonadotropins were found in the urine of this subject in September, 1938. Treatment with 20 mg. of testosterone propionate in oil intramuscularly 2 times weekly beginning

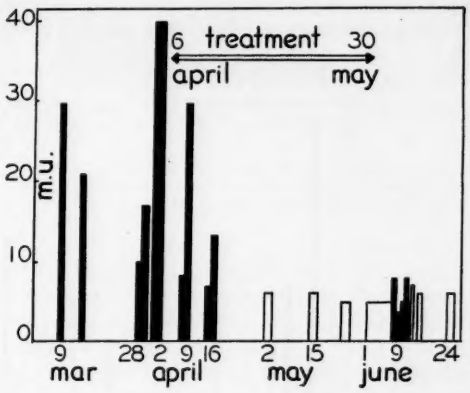

Fig. 3. EXCRETION OF GONADOTROPIC HORMONE IN *case 14* during periods of nontreatment and treatment with testosterone propionate intramuscularly.

in November and carried through Feb. 25, 1939, produced a diminution of the urinary gonadotropins to around 10 M.U. In March, 1940, after 1 year without treatment, preliminary assays showed that the titers had increased to 52 and 70 M.U. The patient then received treatment with 20 mg. of testosterone propionate in oil 5 or 6 times per week, during which time there seemed to be a definite reduction in the urinary values to a mean of 17 M.U. with a range of 5 to > 40 M.U. Thus the treatment was apparently inadequate to secure complete suppression of pituitary gonadotropin output, and it is noteworthy also that this dosage was only partially successful in abolishing the clinical symptoms of castration.

Case 14 (*fig. 3*). Initial assays prior to treatment of this patient showed gonadotropin values ranged from 10 to 40 M.U. Following inception of treatment with 20 mg. of testosterone propionate intramuscularly 5 to 6 times weekly, gonadotropic activity had disappeared from the urine before the end of the fourth week of treatment. Eight days after cessation of injections the urine titer remained negative, with small amounts reappearing inconstantly in the course of the next two weeks. It was somewhat unfortunate that this patient was selected for numerous determinations, since the relatively low castrate values precluded the more extensive changes usually observed upon administration of hormone and upon withdrawal of treatment.

Case 16 (*fig. 4*). Preliminary assays in January, 1938, showed titers of urinary gonadotropins ranging from 80

to 240 M.U. Thereafter, during the intramuscular administration of 20 mg. of testosterone propionate daily, high values were recorded for at least the next 10 days; subsequently lower values of 40 to 18 M.U. were encountered. Ten days after cessation of treatment, titers of 60 M.U. were recorded. High values continued unabated during a period of oral treatment with 60 to 120 mg. of methyl testosterone daily. For example, at the end of this period (April 22nd) titers of 140 and 160 M.U. were observed. Within 2weeks after the beginning of daily intramuscular injections of 20 mg. of testosterone propionate, values for urinary gonadotropins were reduced to less than 20 M.U.

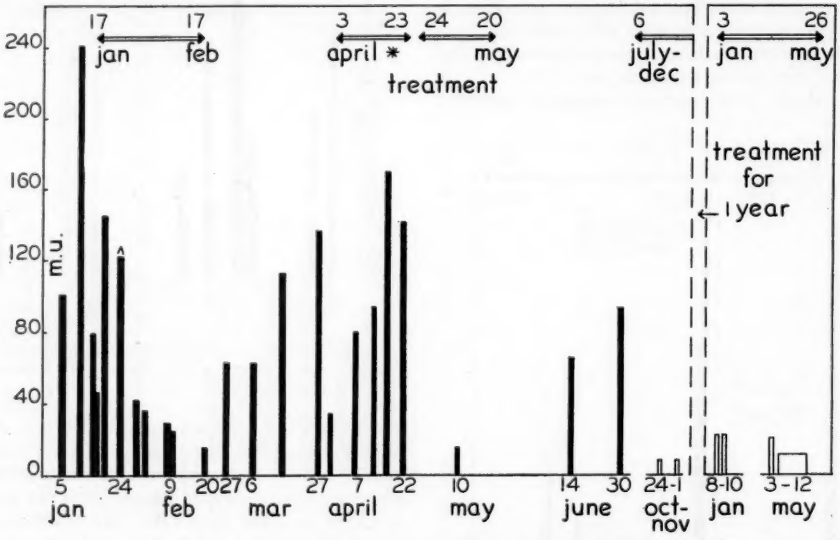

Fig. 4. EXCRETION OF GONADOTROPIC HORMONE in *case 16* during periods of nontreatment and treatment with testosterone propionate intramuscularly, and with methyl testosterone given orally (*).

Twenty-five days after the last injection, values of 75 to 95 M.U. were recorded. From July 6th to September 11th the patient was placed upon a daily maintenance dose of 20 mg. of testosterone propionate, intramuscularly. As this quantity failed to provide satisfactory clinical control, the dosage was increased to 40 mg. on September 12th and assays in late October and early November, 1938, showed urinary gonadotropin titers of less than 10 M.U. Thereafter a dosage of 30 mg. was found to be satisfactory, and this was continued for a period of one year. On Dec. 20, 1939, treatment was discontinued for 13 days, and was begun again on Jan. 3, 1940. On January 8th and 10th the urinary gonadotropic hormone titer was still negative, and during 9 consecutive days in May of the same year consistently negative values (less than 6 M.U.) were recorded.

DISCUSSION

Since the work of Hamburger (14, 15) it has been known that castrate men may have supranormal titers of urinary gonadotropins, but as quantitative measurements are few the typical quantities and range are not well known. Hamburger (15) injected whole urine in mice and employed vaginal smears and ovarian histology as criteria of gonadotropic activity. He found in a series of 14 castrate subjects that 10 excreted between 100 and 500 M.U. per liter, 3 had undetectable amounts and 1 showed between 0 and 300 M.U. per liter. His technique would not appear to permit recognition of quantities of hormone much less than 100 M.U. per liter.

All six men described in the present report as well as four other men castrated prepubertally[3] have excreted quantities of gonadotropins generally greater than those observed in normal men. Our data show that there exists great variability from individual to individual, and from day to day in a single person. Thus *case 14* excreted quantities varying from 10 to 40 M.U., *case 11* from 30 to 140 M.U., and *case 16* from 40 to 240 M.U. We have found the daily excretion in normal males to be between 7 and 20 M.U. The state of general health may affect gonadotropic titers as it does the excretion of steroid substances (16, 17), but the great degree of variation during periods when the men were not ill suggests that other factors are operative in the production of deviations that exceed in some instances any probable inaccuracy due to technical procedures.

The therapeutic use of androgens in men with primary testicular insufficiency (cf. (18) for review) brings about a diminished excretion of urinary gonad-

[3] Hamilton and Catchpole, unpublished data.

otropins. Since in animals the gonadotropic content of the pituitary is increased in castrates (19, 20) and decreased under the influence of androgens (21), it seems reasonable to suppose that alterations in urinary gonadotropins of castrate men under similar circumstances reflect changes in pituitary function. Androgenic therapy can cause lowering of the urinary gonadotropic titer from the supernormal castrate level to within the normal range, or even to amounts too small to be detected (less than 6 M.U. in this series). Continued reduction of gonadotropin titers to approximately the normal range was accomplished in *case 12* by approximately 100 mg. of testosterone propionate per week, given intramuscularly as 5 divided doses. *Cases 14* and *11*, receiving larger doses of 120 to 140 mg. of testosterone propionate weekly in 6 or 7 divided doses, gave evidence of further inhibition of pituitary secretion, the urinary gonadotropin titers being reduced below normal levels. A condition of equilibrium obtains between circulating steroid hormones and the secretion of gonadotropins which is well shown in occasional 'escape' values for gonadotropins (*case 11*), and in the incomplete suppression of gonadotropic excretion that occurs during minimal or subminimal therapy (*case 12*). The daily dosage of androgen required to suppress the hyperexcretion of gonadotropins in the castrate lies between 30 mg. and something less than 20 mg. of testosterone propionate, when administered intramuscularly in 1.0 cc. of peanut oil. Individual requirements vary considerably. On the basis of clinical benefit, *case 16* was found to respond best to 30 mg. of testosterone propionate daily, whereas management of all other cases was achieved with 20 mg. daily. This latter dose is smaller than the quantity (25 mg. daily) ordinarily advocated for the treatment of castrates (22). Use of this amount in castrate men was accompanied by an increase in body weight, muscular growth and cardiovascular changes, and increased stamina, endurance and erectile ability. Further work is necessary to determine whether sexually immature men, who have reached the third decade or more, require for induction of sexual development a larger dose of androgen than that needed to maintain in postpubertal castrates a previously established stage of development.

Implantation of testosterone propionate subcutaneously in the form of pellets has been advocated as an economical procedure (23). In *case 11* 280 mg. of testosterone propionate in the form of cylindrical pellets with a total surface area of approximately 800 sq. mm. was implanted on June 30, 1938. Satisfactory clinical relief was obtained and urinary gonadotropin titers were reduced to normal or subnormal values (fig. 1). Details concerning the type of pellets and the excretion of urinary androgens are given elsewhere (24).

A limited series of observations were made when methyl testosterone was given orally. *Case 16* continued to have elevated urinary titers of gonadotropic hormone during a 20-day course of treatment with

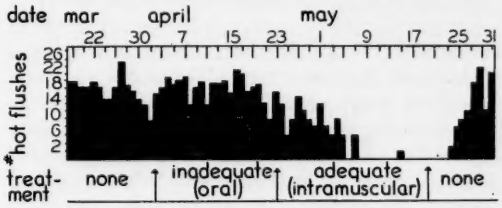

Fig. 5. CHART OF THE NUMBER OF HOT FLUSHES recorded in *case 16* during periods of nontreatment, treatment with methyl testosterone orally and with testosterone propionate given intramuscularly.

from 70 to 100 mg. daily of this substance; no relief of symptoms occurred. However, as already noted the therapeutic requirement of injected testosterone propionate for this patient was higher than in others of our series. Greater success was obtained in *case 11* who received 70 mg. of methyl testosterone daily for 2 months. Both clinical relief and pituitary suppression were apparent.

Following the initiation of effective treatment, that is, treatment which will control clinical symptoms and eventually cause the disappearance from the urine of measurable quantities of gonadotropins, a decreased excretion of hormone was usually seen after 10 or 13 days, with more or less complete disappearance within 3 weeks. We attempted to use the smallest dosage compatible with clinical relief and it is conceivable that with more energetic treatment these time relations would be shortened. By continuing treatment at the maintenance level, inhibition of pituitary function may apparently continue indefinitely. Urine from *case 16* gave negative tests for gonadotropins for 10 consecutive months, the longest period of treatment during which bioassays were made.

In every instance in which urinary gonadotropins had disappeared during courses of androgenic therapy there was a reappearance after cessation of treatment, in amounts as high as those observed prior to therapy. Such return to high levels has been noted after 3-month periods of intensive androgenic therapy, and to this degree at least therefore, the suppression of pituitary gonadotropic function is reversible.

In *case 11*, following incomplete disappearance of gonadotropic hormone from the urine there was a definite increase 7 days after cessation of treatment. In *case 14* the gonadotropic hormone reappeared in

the urine 7 days after treatment was stopped, but a few days later the titer was again negative. The exact time relations of the recovery process are obscured by the possibility of residual amounts of hormone remaining at the injection sites.

As an approach to the problem of obtaining more objective and quantitative analysis of the effects of androgen therapy in castrate men, we have charted the number of hot flushes experienced daily by these individuals. In figure 5 the findings in *case 16*, covering a 2½ month period, may be compared with the corresponding period of therapy and hormone assay charted in figure 4. Hot flushes continued unabated during a course of treatment with 70 to 100 mg. of methyl testosterone daily given orally, but were promptly alleviated by intramuscular injections of testosterone propionate. The occurrence of hot flushes is thus related to androgenic treatment and this may be correlated to some extent with the control of gonadotropin excretion. However, we do not believe that body levels of gonadotropic hormone are causally related to vasomotor instability. Upon institution of androgenic therapy hot flushes may disappear before values of urinary gonadotropins are substantially altered, and upon cessation of therapy hot flushes may reappear promptly even before gonadotropic excretion values return to normal levels. A similar dissociation of gonadotropic titers and vascular changes has been reported in women (8, 25). Furthermore, we feel that a psychogenic factor is important in several of our patients with the most severe vascular disturbances; clinical benefit from androgenic therapy was often less during periods of stress.

SUMMARY AND CONCLUSIONS

1. Men with primary testicular insufficiency excrete amounts of urinary gonadotropins that are generally greater than those of normal men. Both individual and day to day variations are considerable, the range of values being from near normal to eight or ten-fold normal.

2. Testosterone propionate administered in therapeutic dosages reduced the excretion of urinary gonadotropins to undetectable amounts (less than 6 M.U. per 24 hours). Significant diminution in gonadotropic hormone excretion occurred within 10 to 13 days after the beginning of treatment, and with continued treatment the urine remained free of gonadotropins for as long as the study continued (10 months).

3. Following cessation of 3-month courses of androgenic therapy, gonadotropic titers rose to levels observed prior to treatment, detectable amounts being seen after 7 to 13 days. Thus no permanent impairment of this mechanism has been demonstrated.

4. There is no evidence of a direct relation between gonadotropic titers and the incidence of hot flushes or vasomotor instability in men with primary testicular insufficiency.

5. Although in one case 30 mg. of testosterone propionate was required for clinical benefit and control of excessive excretion of gonadotropins this was usually accomplished with a daily dose of 20 mg. of testosterone propionate injected intramuscularly in 1.0 cc. of peanut oil. This dose is about four-fifths of that usually recommended. Control of symptoms and gonadotropic excretion was obtained in one castrate patient with 70 mg. daily of methyl testosterone administered orally.

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Vasomotor Reactions Persisting for Twenty Years in a Male
Treatment with Androgens
[Flushing and Male Hypogonadism]

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RHYTHMIC VASOMOTOR REACTIONS, analogous to those which occur in the menopause, are quite rare in the male. In the case to be reported here,[1] flushes associated with profuse perspiration first began following testicular atrophy that supervened on a bilateral herniorrhaphy. The disturbances occurred approximately every half-hour and the syndrome persisted for twenty years. Under adequate androgen therapy[2] the flushes and sweating disappeared; they recurred whenever the dosage was reduced below the maintenance level.

CASE REPORT

S.H., a 52-year-old unmarried white male, a former resident of Austria, bookkeeper by trade, was first seen on Aug. 18, 1940. He complained of flushes and perspiration which occurred about every half-hour and were so severe that they interfered with his work and embarrassed him socially. Twenty-five years previously he had received roentgen therapy under the chin and to the pubic region for a dermatitis that had resisted other therapy. Following this the hair in both regions fell out and did not grow back. He noticed no change in the size of his testicles at this time nor was there any diminution in libido or potency. Five years subsequently he was operated in Vienna for a bilateral inguinal hernia. Following the operation, according to the patient, he had a hemorrhage into the scrotum which was drained. Shortly after recovery from the herniorrhaphy he noticed that his testicles had diminished in size to about that of the tip of his index finger, and he thought that subsequently there was some loss of libido and potency. About this time he first began to have flushes which lasted about two or three minutes at a time and recurred at the intervals already indicated. For the ensuing 18½ years the syndrome, so far as he could tell, remained more or less constant; he received no therapy. Shortly after coming to America in 1939 the flushes became more severe (though not more frequent); at the time of his first examination he felt them to be almost incapacitating. He had been treated about eight months previously for pansinusitis and atrophic rhinitis.

Examination. His height was 63 inches, his weight was 139½ pounds. The general contour of the body appeared feminine, with excessive deposition of fat over the hips, a protuberant abdomen, and gynecomastia. The skin was smooth; pubic and axillary hair were almost completely absent and there was an area of alopecia under the chin. There was no palpable enlargement of the thyroid. The penis and scrotum appeared normal but testicles could not be palpated; there was a long transverse scar just above the pubis. Except for the sinusitis and atrophic rhinitis already mentioned, there were no other abnormalities. The blood pressure was 140/80 mm. Hg; fasting blood sugar, 75 mg. per cent; basal metabolic rate, +10.

Treatment. The patient was first given testosterone ointment for percutaneous administration of 4 mg. and later 8 mg. of the steroid a day. This produced a noticeable increase in libido but had no effect on the flushes. Subsequently he received 25 mg. of testosterone propionate in oil intramuscularly twice a week together with testosterone from 4 to 8 mg. a day percutaneously for one month. There was gradual diminution in the frequency and duration of the flushes until at the end of the month he had only one or two fleeting reactions a day. He felt definitely stronger, and he noticed a considerable increase in libido and potency. He gained 7½ pounds.

The patient then received 10 mg. of methyl testosterone orally three times a day in place of the injections previously given, at the same time continuing 8 mg. of testosterone per day percutaneously. At the end of two weeks he was completely free of flushes and reported that he had spent 5 hours in a very warm and crowded room without a single reaction; formerly this environment would have been intolerable.

Because a further supply of testosterone propio-

Received for publication December 16, 1941.

[1] I am indebted to Dr. Edwin G. Langrock for permission to investigate this case.

[2] The androgens used in this study, with the exception mentioned in footnote 3, were supplied through the courtesy of Dr. W. H. Stoner of the Schering Corporation, Bloomfield, New Jersey.

nate or methyl testosterone was not immediately available, for the ensuing three weeks he used only the testosterone ointment, 8 mg. of the steroid per day. At the end of this time the flushes had recurred and were appearing irregularly from every half to two or three hours.

Small pellets of methyl testosterone, prepared under a pressure of 6900 pounds per square inch, were then implanted.[3] Using the method described by G. R. Biskind (1) 16 pellets weighing a total of 150.7 mg. were inserted through a long No. 12 hypodermic needle by means of a stylet into the subcutaneous tissue of the outer aspect of the right thigh on Jan. 24, 1941. All other androgenic therapy was discontinued.

Unfortunately, at about this time the patient acquired influenza. Shortly after recovery from the attack he complained of a sore mouth and lips and was found to have a stomatitis with the purplish-red fissured tongue and the typical fissures at the corners of the mouth indicative of a predominant riboflavin deficiency. This was treated with large doses of brewers' yeast, a preparation of vitamin B complex derived from yeast and liver, riboflavin, nicotinic acid, fresh liver and parenteral crude liver extract. Later, when nicotinamide became available, it was substituted for the nicotinic acid, as the vasomotor reactions produced by the latter drug appeared to confuse the clinical picture; the patient spontaneously reported moderate improvement in the flushes promptly after this change was made. The oral lesions improved slowly, but were still detectable after several months of continuous treatment with large doses of the specific substances. Exacerbations occurred whenever he caught a cold or was under unusual stress. The blood picture was normal.

After implantation of the pellets, for about 10 days or two weeks there were no flushes or only one or two a day. Then they became gradually more frequent, occurring every 1½ to 3 hours. After about a month the pellets were no longer palpable although, judging from the lessened frequency of the flushes, some androgen was probably still present.

Injection of 25 mg. of testosterone propionate in oil intramuscularly twice a week again caused complete cessation of symptoms after five weeks. Again, when it became necessary to interrupt therapy the syndrome returned to its original status; within three weeks the patient was having flushes every half hour.

On June 20, 1941, four 75 mg. pellets of testosterone (total 300 mg.) were implanted through a small incision subcutaneously in the upper left gluteal region. Healing occurred rapidly and there was no local tenderness. Prompt improvement in the flushes followed (mild reactions occurred about every two or three hours) but this amount of androgen was insufficient entirely to control the symptoms. Judging from recent reports (1, 2) probably two or three times the amount implanted would be necessary. The pellets were still palpable 3½ months later, at which time the symptoms, while present, were so mild and infrequent that he ceased complaining about them. The androgen therapy caused no change in fat distribution and the gynecomastia was unaffected. While the sinusitis had improved there was no change in the atrophic rhinitis. No significant change occurred in the basal metabolic rate.

[3] These were kindly supplied by Dr. Gerson R. Biskind of Mt. Zion Hospital, San Francisco, California.

SUMMARY

An unusual case is reported of rhythmically recurring flushes persisting for twenty years in a male with secondary hypogonadism. The flushes disappeared under adequate androgen therapy and recurred whenever dosage was reduced below the maintenance level.

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The Use of Male Sex Hormone in Endocrine Disturbances in Children

[Androgens and Genital Development]

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MALE SEX HORMONE has rarely been used in the treatment of endocrine disturbances in children. Since the first reports on the use of male sex hormone there has been the fear and the danger of side effects. Male sex hormone definitively produces profound anatomical changes, such as the growth of the penis, scrotum, seminal vesicles and prostate, as well as the development of pubic and axillary hair and the hair on the extremities. There is a marked change in the texture of the skin and in addition there is an improvement in the general well-being and personality with the use of this hormone. Kenyon (1) reports that its use brings about a retention of nitrogen and sodium and a slight increase in the basal metabolic rate. Moore and Price (2) hypothesized that the sex hormones cause atrophy of the gonads by inhibition of the gonadotropic hormone of the pituitary. Recently Zelson and Steinitz (3) stated that the male sex hormone will produce an enlargement of the penis and scrotum and growth of pubic hair, but will also cause a shrinkage in the size of the testicle descended and undescended. Shay and his collaborators (4) state "the immature germinal epithelium can be stimulated by testosterone propionate to increased activity but not to an earlier maturation. Once a stage is reached at which maturation intrinsically becomes possible, testosterone propionate may stimulate maturation quantitatively. The treated animals' testes then carry more mature spermatozoa than those of the controls." They found that treating young rats with large doses of testosterone propionate causes less inhibition of growth and sperm maturation than small doses. They tentatively explain their findings thus: "Testosterone propionate is thought to stimulate the testes directly, at the same time exerting an inhibitory influence on the pituitary. This in turn inhibits the testes through inhibition of the gonadotropic pituitary hormone. During the first month of life the stimulating effect is not counteracted by inhibition of the pituitary because gonadotropic function is not yet developed. Very large doses are necessary to make the stimulating effect dominant, or in other words the pituitary is more sensitive to testosterone than the testes." The reciprocal influence of the pituitary and gonad secretions seems to be one of the principal regulatory factors in the hormone secretion.

In our present state of knowledge it is impossible to state when the male sex hormone secretion is first established (5). It has been hypothesized that embryonic development of the Wolffian ducts is conditioned by secretion from the embryonic testis. Moore, in his microscopic studies on the human prostate, suggested a temporary flush of hormone secretion at birth (perhaps this is due to maternal hormones), a lower grade of secretion sufficient to cause slow growth of the prostate to about 10 years of age, then a rather sudden rush of more active secretion at puberty, a constant active secretion until the fifth and sixth decade and then a gradual diminution of hormone production. Nathanson and his associates (6) report that from 3 to 7 years of age, both boys and girls excrete a small and constant amount of estrogens and 17-ketosteroids in the urine with very little difference between the sexes. From 8 until 11 years there is an increased secretion of these hormones, the estrogens in the girls and the 17-ketosteroids in the boys. There is higher excretion of 17-ketosteroids in boys after 11 years of age. The follicle-stimulating hormone appears in the urine of boys between 12 and 13 years of age.

It seems logical to believe in the theory of Shay that there will be only a stimulative effect on the testes in children, since the gonadotropic function of the pituitary is not yet developed and so no inhibitory activity can occur.

The results in the treatment of cryptorchidism with male sex hormone have been no better than with other endocrine products. The percentage of descent varies roughly from 10 to 80 (7). Zeithaml (8) re-

Received for publication December 3, 1941.

ported that in 8 patients with 10 undescended testicles treated with testosterone propionate no change was noted in the testes. These received from 17.5 to 145 mg. In none of these patients studied was there an observable effect on growth or body build. Zelson and Steinitz (3) reported on 20 children between 7½ and 13 years of age. Eleven had had previous treatment with gonadotropic hormone varying between 5100 and 40,000 U. There was complete descent in 15 per cent and partial descent in 45 per cent. One boy grew one-half inch and one grew 1 inch in four weeks. Subsequently (9) these authors reported on the treatment of cryptorchidism with combinations of anterior pituitary-like substance and testosterone, 53 per cent responded with complete descent of the testes.

Fourteen cases of endocrine disturbances which were treated with male sex hormone ointment[1] and oral methyl testosterone[1] are here reported. There were 5 patients with 5 undescended testicles, 7 with infantile genitalia, 1 case of hypogonadism and 1 of atrophy of a testicle following mumps.

CASE REPORTS

Case 1. W.L., a 10½-year-old boy, was admitted on Dec. 4, 1940, to the Pediatric Endocrine Clinic with the complaints of undescended testicles and obesity. Physical examination revealed the right testicle undescended; the left was descended but was small and soft; the penis was small and there was a female distribution of fat. The B.M.R. was −3; roentgenograms of the sella and the epiphyses revealed normal structure. The weight was 127 lb., the height 61 inches. He was given gonadotropic hormone,[2] 10 U twice weekly and received a total of 210 units with no improvement. On May 3, 1941, he was given 4 mg. of testosterone propionate by inunction six times a week. On June 21, 1941 the penis had increased in size, pubic hair had become abundant, the left testicle was much larger and firmer, the right testicle was still undescended, the weight was 128 lb. and the height 63 inches.

Case 2. J.G., a 7½-year-old boy was admitted on Feb. 10, 1941, to the Pediatric Endocrine Clinic. Physical examination revealed an obese child with a minute penis and a right undescended testicle. The B.M.R. was +2 and roentgenograms showed no abnormalities in the osseous centers. He was given methyl testosterone, 10 mg. once daily. On June 14, 1941, his condition was unchanged. However, his height was now 54 inches and his weight 92 lb. while on admission his height had been 52½ inches and his weight 89 lb.

Case 3. A.F., a 10-year-old boy, was admitted on Feb. 17, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed an obese boy with a small penis and a right undescended testicle. His weight was 103 lb. and his height 54½ inches. He was given testosterone propionate, 10 mg. weekly for four months. On Sept. 7, 1940, the right testicle was still undescended, the penis was larger, the pubic hair profuse. The B.M.R. was −1 and roentgenograms showed a slight delay in the epiphyseal centers of both pisiform bones. He was treated with testosterone propionate again for one month. On Nov. 23, 1940, there was no improvement. His weight was 120 lb. and height 57¾ inches. He was then given testosterone propionate by inunction. On Feb. 15, 1941, there was marked growth of the penis, pubic hair had increased, the left testicle was firmer, the right was not felt. On March 21, 1941, both testicles were descended. His weight was 121 lb. and his height 58½ inches. When last seen in September, 1941, the testicles were still descended.

Case 4. H.B., an 11-year-old boy, was admitted on Nov. 28, 1939, to the Pediatric Endocrine Clinic. Physical examination revealed a left undescended testicle. His height was 60 inches and weight 94 lb. He received anterior pituitary-like hormone 500 U twice weekly for one year with no results. On Oct. 5, 1940, he was given testosterone propionate, 10 mg. weekly. His height at this time was 61 inches and weight 103 lb. He received treatment for one month with no improvement. He was then given testosterone propionate by inunction in addition. On March 22, 1941, there was no descent of the testicles noted. His height was 64 inches and his weight 108 lb. Therapy was discontinued.

Case 5. I.P., a 7-year-old boy, was admitted on May 25, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed a left undescended testicle. His weight was 64 lb. and his height 49½ inches. He was given anterior pituitary-like hormone, 150 U twice weekly for three months with no improvement. On Sept. 14, 1940, he was given testosterone propionate, 10 mg. weekly. His weight was 62 lb. and his height 50½ inches. The roentgenogram showed the epiphyses were normal. On May 3, 1941, the testicle was still undescended and the patient was given testosterone propionate by inunction. His weight was 76 lb. and his height 52½ inches. On June 14, 1941, the testicle was still undescended. The weight was 74 lb. and the height 54 inches.

Of these five cases of cryptorchidism only one cryptorchid testicle descended. However, four of these boys showed an abnormal rate of growth and the other showed marked improvement of the secondary sex characteristics.

Case 6. F.M., a 16-year-old boy, was admitted on April 14, 1939, to the Pediatric Endocrine Clinic. Physical examination revealed a typical eunochoid. The breasts were large and fatty. The penis and testicles were very small. There was no body hair. The voice was high-pitched. The height was 64 inches and the weight 119 lb. The Wassermann reaction was 4+. He was given an anterior pituitary-like substance until Nov. 4, 1939, with no improvement resulting. His weight was now 127 lb. and his height 66¾ inches. He was given testosterone propionate, 10 mg. three

[1] The testosterone propionate (Perandren) and the methyl testosterone (Metandren) were supplied by the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

[2] Pregnant mare's serum.

times weekly and this was then increased to 25 mg. three times weekly. By February, 1940, he had received about 375 mg. of testosterone propionate. There was definite increase in the size of the penis, some pubic hair was visible and the voice was lower pitched. On July 30, 1940, his height was 69 inches and his weight 132 lb. The penis had further increased in size, pubic and axillary hair was present and there was a fine fuzz on his cheeks. The B.M.R. was −3. On March 1, 1941, his height was 72 inches, his weight 142 lb. He had had no therapy for one month because of interstitial keratitis. The testicles were firm but small, the penis was normal, there was abundant hair in the pubic and axillary regions and he was shaving once a week. He was given oral methyl testosterone 10 mg. three times a day and this was later reduced to 10 mg. daily. In September, 1941, his condition was excellent.

Case 7. G.K., a 9-year-old boy, was admitted on Dec. 7, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed a right atrophic testicle which had followed an attack of mumps. The testicle was the size of a lima bean. The patient was given testosterone propionate, 10 mg. twice weekly, for one month without results. He was then given the injections once weekly in addition to testosterone propionate ointment. In April, 1941, his general condition was good. The B.M.R. was −1 and roentgenograms of the epiphyses showed them to be normal. The atrophic testicle had increased until it was the size of a small walnut. The patient was discharged. His height on admission was 60 inches and at discharge 60½ inches.

Case 8. L.S., a 13½-year-old boy, was admitted on March 2, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed small genitalia, no pubic hair and a high-pitched voice. He was given testosterone propionate, 10 mg. twice weekly for two months, with no change. On April 19, 1941, the genitalia were unchanged in appearance and the patient was given oral methyl testosterone, 10 mg. daily. On May 24, 1941, the genitalia had increased markedly in size.

Case 9. P.S., a 12-year-old boy, was admitted on Jan. 10, 1939, to the Pediatric Endocrine Clinic. Physical examination revealed bilateral undescended testicles. He received anterior pituitary-like hormone three times weekly. On May 16, 1940, both testicles were descended. He was seen again March 1, 1941 and this time the genitalia were small and the testicles soft. He was given testosterone propionate, 10 mg. weekly for three months with no change resulting. On June 7, 1941, he was given oral methyl testosterone, 10 mg. every other day. In September, 1941, there was no change noted.

Case 10. T.B., a 10-year-old boy, was admitted on May 8, 1939, to the Pediatric Endocrine Clinic. Physical examination revealed infantile genitalia. A roentgenogram showed slight delay in the appearance of the pisiform bone. He received anteroir pituitary preparations without results. After six months during which he received no treatment he was given testosterone propionate, 25 mg. weekly for three months which resulted in an increase in the size of the penis but not in the testicles. On April 19, 1941, his condition was unchanged and he was given oral methyl testosterone, 10 mg. daily. His height was 59¾ inches, his weight 112 lb. By June of 1941, the testicles had increased in size. His height was 61 inches and his weight 113½ lb.

Case 11. J.D., a 9-year-old boy, was admitted on Feb. 8, 1939, to the Pediatric Endocrine Clinic where he received gonadotropic hormone for undescended testicles which descended following therapy. He returned to the clinic because of very small genitalia and received anterior pituitary-like hormone, 500 U twice weekly for one year, without improvement. On Dec. 14, 1940, he was given testosterone propionate by inunction. By June, 1941, the genitalia showed a marked increase in size and therapy was discontinued.

Case 12. H.S., an 8-year-old boy, was admitted on May 28, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed small genitalia. The B.M.R. was −1. He was given an anterior pituitary extract twice weekly for five months without improvement, and then was given anterior pituitary-like hormone, 500 U twice weekly for two months, without improvement. On Feb. 15, 1941, the testicles were small and soft and receded easily. He was given oral methyl testosterone, 10 mg. daily. On June 28, 1941, the genitalia were normal in size; both testicles were firm and large and did not recede.

Case 13. F.C., a 15-year-old boy, entered the Clinic because of short stature and infantile genitalia. His weight was 81 lb. his height 54¼ inches. Roentgenograms showed a delayed development of the osseous centers of both wrists. He received an anterior pituitary preparation for eight months without results. On Sept. 21, 1940, he was given testosterone propionate, 10 mg. weekly. His height at this time was 56 inches. He received the injections until Jan. 4, 1941. The genitalia were still small, there was no change in the body hair and the voice was still high-pitched. However, there was a marked improvement in the general condition. The boy was more cheerful, more active and brighter. A roentgenogram showed generalized hypo-development of the bones of both hands. Treatment was stopped. On March 15, 1941, the boy was seen again. He was tired, nervous and irritable and the skin was very dry. He was given testosterone propionate by inunction. On June 28, 1941, his general condition was good, the genitalia had increased markedly in size, the skin was moist and smooth and therapy was stopped. His height at this time was 57 inches and his weight 85 lb.

Case 14. M.T., a 6-year-old boy seen in the Pediatric Endocrine Clinic on Jan. 25, 1941. Physical examination revealed obesity with infantile genitalia and alopecia areata. His weight was 94 lb. and his height 52½ inches. He was given gonadotropic hormone, 10 U twice weekly. On May 5, 1941, there had been no change in his condition. His height was 53 inches and his weight 102 lb. The B.M.R. was +7 and the roentgenogram showed no delay

in ossification. He was given testosterone propionate by inunction with no results after one month.

In our use of male sex hormone in children we have been particularly impressed with certain factors. One is the lack of any side effects which we were particularly careful to check. In no instance was there any complaint of priapism or ejaculations, diurnal or nocturnal. In only one case were there nocturnal ejaculations (*Case 6*), and we considered this result more therapeutic than otherwise.

Another striking factor was the ease of administration and the willingness of the patients to take this form of therapy. There has always been difficulty in getting children to return regularly for injections so that therapy by the intramuscular method had never been continuous. With the use of the ointment and tablets the children were much more cooperative and the dosage was easier to regulate.

The last factor which impressed us was the effect on the rate of growth in a number of these boys. In four there was a definite increase in the rate of growth over the normal. In none of the patients on whom roentgenograms were made was there premature closure of the epiphyses noted.

SUMMARY

Fourteen males, 16 years of age and younger, with endocrine disturbances, were treated with testosterone propionate by inunction and with oral methyl testosterone and Metandren.

We have found the use of ointment and tablets by mouth more efficacious than intramuscular treatment in children.

No deleterious side effects were noted.

Seven boys with infantile genitalia were treated and 5 were so improved that they were discharged. Five cases of cryptorchidism were treated; only 1 cryptorchid testicle descended. Four of these boys showed an increased rate of growth. One atrophic testicle was increased in size. One eunuchoid patient improved remarkably on the therapy employed.

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COMMUNICATIONS TO THE EDITORS

Goiter, Iodine and Military Strength. II.

Since goiter reduces military strength, its cause and distribution should be of interest at this time. The first communication[1] of the series supports the iodine-deficiency theory of its origin but many physicians still consider the cause of goiter to be unknown. Few analyses of iodine in drinking water have been made, therefore the relation of iodine to geological formations is considered.

A reduction in goiter incidence in areas over petroleum and salt deposits has been noted.[2] The salt is usually formed by the evaporation of impounded sea water, but smaller deposits may arise from these by solution, transportation and re-evaporation. Petroleum is often underlaid by brine and the frequency of its association with brine or salt might indicate its marine origin. An area of salt and petroleum is not uniform throughout, there being many gaps in the layers of both salt and petroleum, which would require close spacing of expensive drilling for complete mapping. Owing to its greater commercial value, the petroleum areas have been explored more thoroughly than the salt. The salt came from the ocean which is calculated to contain about 65 billion tons of iodine, and since this remains soluble after the water is evaporated, marine deposits are a valuable source of iodine to land organisms. Rocks contain more iodine per volume than sea water and some of the iodine released by weathering is retained in the soil. Soils are richer in iodine than the rocks from which they are formed. But this source of iodine alone is not sufficient to prevent goiter.

The Texas Panhandle (including the adjacent region) is unique in that the petroleum has proven valuable and a valuable deposit of potash has been the incentive for still more drilling. There are two potash mines 1000 and 1800 feet deep near Carlsbad, New Mexico tapping the earth beneath the deepest part of the sea that existed in the Permian period. The axis of this Permian deep extends northeast through the Texas Panhandle and western Oklahoma into Kansas. Salt is encountered about 700 feet below the surface and in some places it extends to about 11,000 feet.[3,4] To account for this great thickness (since ocean water is only 3.5% total solids) it is supposed that this Permian sea maintained a connection with the ocean which fed in more water as it evaporated. From the area of the deposits (about 100,000 square miles) and the ratio of iodine to salt in sea water, it may be calculated that the deposits contain about 30 million tons of iodine—on the basis of McClendon's analysis of the iodine content of ocean water (50 parts per billion).[5]

Although the iodine together with the common salt is brought to the surface mainly by artesian wells and springs, many of these springs have become impounded and form 'alkali lakes' over the axis of the salt deposits. Salt has been commercially obtained in the Texas Panhandle and Kansas for a long period.

Table 1. Iodine and chlorine[6] content of mineral waters in Kansas
(*parts per million*)

Locality	Chlorine	Iodine	Locality	Chlorine	Iodine
Abilene	110,000	6.3	Rosedale	14,000	1.0
Arkansas City	19,000		St. Paul	17,000	
Atchison	16,000		Greenwood Co.	6,900	
Eureka	4,390		Allen Co.	16,700	
Fredonia	49,000	8.4	Wyandotte Co.	25,700	
Geuda Springs	11,000		Meade Co.	42,800	
Independence	45,000	1.3	Douglas Co.	49,700	
Lawrence	30,000		Barton Co.	54,500	
Leavenworth	16,000		Pawnee Co.	57,800	
Marion	33,000		Montgomery Co.	59,400	
Mound City	10,000		McPherson Co.	187,000	

Table 2. Iodine in drinking water
(*parts per billion*)

Permian salt area		Points in surrounding states	
Lincoln, Neb.	0.05	Ames, Iowa	0.012
Independence, Kan.	0.06	Iowa City, Iowa	0.015
Hutchinson, Kan.	0.10	Bozeman, Mont.	0.015
Lawrence, Kan.	0.10		
Ft. Scott, Kan.	0.66		
Kansas City, Kan.	1.69		
Salina, Kan.	3.91		

Table 3. Frequency of large goiters per 1000 drafted men in World War I

States containing Permian salt		Surrounding states	
Texas	0.30	Colorado	5.29
New Mexico	0.88	Wyoming	15.37
Oklahoma	0.72	Montana	21.00
Kansas	1.25	South Dakota	4.09
Nebraska	2.14	Iowa	6.68
		Missouri	3.99

[1] McClendon, J. F., and W. C. Foster: *J. Clinical Endocrinology* 1: 187. 1941.
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[5] McClendon, J. F.: *Science* 56: 269. 1922.
[6] The University Geological Survey of Kansas: 7. Mineral Waters 68. 1902.

The analyses of these springs (mineral waters) in Kansas for chlorine and iodine are given in table 1.

The chlorine content of the water supply of 146 cities and towns in Kansas averages 68 parts per million whereas in rivers not draining petroleum-salt regions it seldom exceeds 10 parts per million. The Pecos river drains the lower part of the Permian salt area and furnishes the main volume of the Rio Grande river at Laredo, which analyzed 164 parts of chlorine per million. The Arkansas river which drains Kansas averages 203 parts of chlorine per million at Little Rock. The Colorado river of Texas that drains the border of the Permian salt area averages 59 parts of chlorine per million at Austin. The Red River that drains the Texas Panhandle averages 121 parts per million at Shreveport. It is probable that all but about 10 parts of chlorine per million of these rivers came originally from Permian deposits and should contain the iodide occluded by the chloride.

Although the iodine analyses of drinking waters are few, the data in table 2 show a difference between the waters of the Permian salt area and that of surrounding states.[2]

The distribution of simple goiter in the Permian salt area compared with that of the surrounding region necessitates the omission of the southern part of the latter since this southern region was entirely submerged under the sea during several geological periods. With this omission, the number of large goiters per 1000 drafted men[7] during the first world war is shown in table 3.

It seems evident that there is less goiter in areas over the Permian salt deposits than in the surrounding states and this is inversely correlated with the leakage of the deposits (specifically chlorine and iodine) to the surface. This adds support to the iodine-deficiency theory for the origin of goiter but it does not demonstrate that the iodine intake is adequate by individuals living over the Permian salt area, because the incidence of goiter is not zero. The universal use of iodized salt is recommended.

J. F. McClendon, Ph.D.
W. C. Foster, M.S.

From the Research Laboratory of Physiology, Hahnemann Medical College, Philadelphia, Pennsylvania

[7] Love, A. G., and C. B. Davenport: Defects Found in Drafted Men. Gov. Printing Office, 1926. P. 111.

Conservation of Scholarly Journals

The American Library Association has created a Committee on Aid to Libraries in War Areas, headed by John R. Russell, the Librarian of the University of Rochester. The Committee is faced with numerous serious problems and hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

One of the most difficult tasks in library reconstruction after the first World War was that of completing foreign institutional sets of American scholarly, scientific, and technical periodicals. The attempt to avoid a duplication of that situation is now the concern of the Committee.

Many sets of journals will be broken by the financial inability of the institutions to renew subscriptions. As far as possible they will be completed from a stock of periodicals being purchased by the Committee. Many more will have been broken through mail difficulties and loss of shipments, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the Committee already give evidence that it will be enormous.

With an imminent paper shortage attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the Committee hopes to enlist the cooperation of subscribers to this journal in preventing the sacrifice of this type of material to the pulp demand. It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

Questions concerning the project should be directed to Wayne M. Hartwell, Executive Assistant to the Committee on Aid to Libraries in War Areas, Rush Rhees Library, University of Rochester, Rochester, New York.

Abstracts of CURRENT CLINICAL LITERATURE

Editor: DANIEL A. McGINTY. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, EMMERICH VON HAAM.

ADRENALS

LEWIS, R. A., G. W. THORN, G. F. KOEPF AND S. S. DORRANCE.

The role of the adrenal cortex in acute anoxia. *J. Clin. Investigation* 21: 33. 1942.

Five hours of low environmental O_2 tension produced in animals (rat, rabbit, dog, monkey) a depletion of liver glycogen with persistence of normal blood sugar levels, except when anoxia was severe, Twenty-four hours exposure resulted in a rise in blood sugar level, liver glycogen (except in dogs), and increased urinary N, P, Na, Cl, K. The adrenalectomized animal proved incapable of surviving similar low O_2 tensions, and showed no comparable blood or urine changes, save for a marked increase in K excretion. Treatment of the adrenalectomized animals with 11-dehydro-17-hydroxycorticosterone evoked responses similar to those observed in the normal animal. Human subjects showed a decrease in N excretion upon 5 hours exposure to low tensions. The initial phase of anoxia appeared to be accompanied by increased utilization of carbohydrate in the normal subject. Adaptation to prolonged exposure consisted in a rise in protein catabolism. Neither change appeared in the adrenalectomized preparation.—*H.O.H.*

RAAB, W.

Adrenocortical compounds in the blood. Relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure. *Arch. Int. Med.* 68: 713. 1941.

Human blood contains adrenal hormonal compounds consisting of epinephrine and cortical sterols (adrenocortical compounds) and most normal persons showed a level within normal range, as determined by a modification of the colorimetric method of Shaw. Smokers were above the average. Little change in the level was occasioned by exercise in normal persons, in contrast to the marked elevation usually found in patients with essential hypertension after a short period of exercise. An abnormally high level was found in a number of persons with renal hypertension, with congestive heart failure and associated pulmonary edema and particularly in those with renal insufficiency with associated uremia. No clear relation existed between the level of the adrenocortical compounds in the blood and that of the blood pressure. There was a tendency toward a fluctuating mode of secretion of the adrenal glands in essential hypertensive subjects, which could be elicited by physical exercise and probably by other stimuli. The phenomenon furthered the development of arteriosclerosis and resulting ischemia in the vasomotor centers of the brain and in the kidneys, in this way contributing to the two outstanding mechanisms of central and renal hypertension. Adrenocortical compounds probably exerted a damaging effect on the cardiac muscle, in view of the tendency of the myocardium to absorb and to deposit both epinephrine and cortical sterols.—*W. C. Hunter (courtesy Chem. Abstracts).*

RUSSELL, JANE A., AND A. E. SILHELMI.

Glyconeogenesis in kidney tissue of the adrenalectomized rat. *J. Biol. Chem.* 140: 747. 1941.

The formation of carbohydrate from pyruvate and succinate is unimpaired in kidney tissue from adrenalectomized rats, but there is significantly less formed in the presence of *dl*-alanine, *l*(+)-glutamic acid and *a*-ketoglutaric acid. An important factor limiting the rate of glyconeogenesis after adrenalectomy is the rate of deamination of amino acids, but the results with *a*-ketoglutaric acid indicate that it is not safe to assume the indifference of the tissues to the products of deamination of all amino acids. The experiment, will be continued using liver slices.—*A. P. Lothrop (courtesy Chem. Abstracts).*

ENDOCRINE GENERAL

BREMER, J. L.

Osteitis fibrosa localisata. *Arch. Path.* 32: 200. 1941.

Experiments on rats indicated that the general disease may be caused by long continued excess of estrogens, probably acting through the parathyroid glands. The local cysts may result from a temporary excess of estrogens, soon reduced sufficiently to permit renewed normal growth. In this case a small amount of the mesenchymal tissue which is the initial stage of the 'fibrosis' may be cut off within the bone and there undergo any of the changes met with in normal histogenesis, especially those leading to fibrous tissue and cartilage. This condition was reproduced experimentally. These enclosed masses might enlarge, erode vessels, degenerate and liquefy; giant cells might cluster round them as around a foreign body. They might remain dormant for years. As an unusual cariant of this more solid type, the true bone cyst could result

from the rare combination of temporary excess of estrogenic or parathyroid activity with chronic internal pressure in a neighboring joint or bursa. The condition would then resemble almost exactly that encountered in the pneumatization of avian bones. Successful entry of a diverticulum of joint or bursa into the bone might depend on the presence of emergent blood vessels whose loose mesenchymal adventitia could afford a pathway through the dense outer layer of the periosteum. Attempts to reproduce experimentally the proper combination of these circumstances were not successful, but the possibility of such a combination should be considered in any attempt to explain the etiology of human solitary bone cysts.—*J. L. Bremer.*

FREED, S. C., AND E. LINDNER.

The effect of steroids of the adrenal cortex and ovary on capillary permeability. *Am. J. Physiol.* 134: 258. 1941.

Crystalline corticosterone, desoxycorticosterone and commercial adrenal cortex extract were tested for their effect on capillary permeability by Menkin's leucotaxine method. Corticosterone and adrenal cortex extract prevented the action of leucotaxine in increasing the permeability of capillaries. Desoxycorticosterone did not do this but often produced a slight increase in capillary permeability. Estrone, stilbestrol and progesterone failed to prevent the leucotaxine effect but produced an increase in capillary permeability when given alone. The ability of steroids to maintain life in adrenalectomized animals is not necessarily related to their effects on capillary permeability.—*E. D. Walter (courtesy Chem. Abstracts).*

GLEBOVA, M. S.

The importance of the chorion as regards internal secretion. *Bull. biol. méd. expér. U.R.S.S.* 7: 16. 1939.

In addition to considerable amounts of gonadotropic hormones, the fertilized human ovum contains a special ketogenic hormone which probably is identical with the "fat hormone" of the anterior lobe of the pituitary described by Anselmino and Hoffmann. This ketogenic hormone could not be detected in the chorions of hogs and cattle, which contain less and more variable amounts of gonadotropic hormones than human chorions. Tests for the ketogenic hormone were made by determining the content in ketonic substances of the blood of adult male rats. Toxicoses of pregnancy, especially persistent vomiting, are probably due to an increased production of the ketogenic hormone, not in the pituitary, as assumed by Anselmino and Hoffmann, but rather in the chorion.—*M. G. Moore (courtesy Chem. Abstracts).*

HEMPHILL, R. E., AND M. REISS.

Investigations into the significance of the endocrines in involutional melancholia. *J. Ment. Sc.* 86: 1065. 1940.

Endocrine study of 30 female patients, including 15 nulliparae, suffering from depressive illnesses associated with menopause or the involutional state indicated an approximate grouping into: *a*) pure hypo-ovarian, *b*) hypo-ovarian combined with hypothyroidism, *c*) hypo-ovarian combined with hyperthyroidism (7 cases, 6 of whom had borne children), *d*) hypo-ovarian combined with hypo-adrenalism (8 cases). Studies were made of vaginal smears, gonadotropic hormone increase, together with follicular hormone, luteal hormone, and corticotropic hormone treatment. The intimate relationship of pituitary and thyroid through the thyrotropic principle is emphasized; the importance of adrenal insufficiency in certain types of involutional melancholia is stressed; and it is suggested that disturbances of the activity of the anterior pituitary are largely responsible for the protean characteristics of involutional melancholia—*W. L. Wilkins* (courtesy *Psychol. Abstracts*).

LUBIN, S., T. S. DREXLER AND W. A. BILOTTA.

Postpartum pyeoureteral changes following hormone administration. *Surg. Gynec. & Obst.* 73: 391. 1941.

Dilatation of the urinary tract in post-partum women regressed within the first week in half of the subjects. Pituitrin seemed to enhance regression, progesterone to delay it, stilbestrol had no effect. The small number of patients used and the individual variations during a period of rapid physiological adjustment necessitates a tentative attitude toward these data, a point well recognized by the authors.—*A.T.K.*

VON HAAM, E.

Recent progress in endocrinology. *Ohio State M. J.* 37: 625. 1941.

Recent advances are reviewed. Successful separation of the various pituitary hormones, the creation of radioactive I, the isolation of the Na factor in the adrenal cortex and the exploitative investigation of stilbestrol are considered outstanding contributions of practical importance for the medical sciences.—*Ruth Berggren* (courtesy *Chem. Abstracts*).

GONADS

ALBRIGHT, F., ESTHER BLOOMBERG AND PATRICIA H. SMITH.

Post-menopausal osteoporosis. *Tr. A. Am. Physicians* 55: 298. 1940.

Estrin therapy is effective in restoring a positive Ca and P balance in females with post-menopausal osteoporosis.—*M. L. C. Bernheim* (courtesy *Chem. Abstracts*).

ALLEN, W. M.

The chemical and physicological properties, and clinical uses of the corpus-luteum hormone, progesterone. *Bull. New York Acad. Med.* 17: 508. 1941.

A review of the present day knowledge concerning the corpus luteum hormone is presented. Its chemical properties and physiological effects in animals are discussed. Included is a brief survey of the clinical application to women of the various physiological properties of progesterone.—*C. T. Kaylor* (courtesy *Biol. Abstracts*).

BIRCH, C. L.

Assay of the estrogenic hormone in hemophilic and normal male urine. *Proc. Soc. Exper. Biol. & Med.* 48: 167. 1941.

By use of a standard biologic method, 252 assays were made upon the urine of 52 hemophiliacs and normal controls. Of determinations on hemophilic urine 17% were positive, 28% of the determinations on normal urine controls were positive. Estrus per positive rat in both groups was averaged 14 hours. Although the hemophilic group showed a lower per cent of positive reactions the variations in both were so great that the difference is probably not significant.—*C. L. Birch.*

BOYD, E. M., J. W. CLARK AND W. F. PERRY.

Estrogens and their effect on ciliated mucosa. *Arch. Otolaryng.* 33: 909. 1941.

A method is presented for assaying the effect of estrogenic substances on movements of cilia taken from the buccoesophageal mucosa of the frog, by measuring the time required for the cilia to carry a mustard seed 1 cm. Crystalline estrone, estriol and estradiol, dissolved in 0.75 per cent NaCl solution, stimulated ciliary movement when given in minute doses and depressed it in large doses. The range of doses producing stimulation when applied topically was about 7×10^{-2} to 2×10^{-1} mg. estrone per 100 cc. saline solution, 2×10^{-3} mg. estriol, and 7×10^{-5} to 2×10^{-4} mg. estriol.—*Dorothy A. Meyer (courtesy Chem. Abstracts).*

CALCAGNO, B.

Ocular disturbances of the menopause treated with artificial estrogens. *Semana méd.* 48: 657. 1941.

Two cases are reported of severe edematous conjunctivitis associated with general menopausal syndrome. Diethylstilbestrol dipropionate was injected twice weekly at a dose level of 0.5 mg. Complete recovery with subsidence of the menopausal symptoms was obtained after short treatment.—*A.E.M.*

CANTILO, E., AND C. F. SPERONI.

Endocrinopathies. I. Sexual impotence caused by adrenal hypofunction. *Semana méd.* 48: 687. 1941.

Complete loss of libido and sexual potency was found in a 30-year-old male, with concomitant symptoms were anorexia, alternating constipation and diarrhea, discomfort after meals, general lassitude and mental depression. Diagnosis of adrenal insufficiency was borne out by response to treatment which consisted in parenteral application of desoxycorticosterone acetate, vitamins B_1 and C, and a few doses of testosterone propionate. NaCl was given by mouth and the diet was kept low in K. Complete recovery was effected within 2 months.—*A.E.M.*

CATEL, W., AND H. SCHOTOLA.

The relation between thrombocytes, menstruation and the corpus luteum hormone. *Med. Klin.* 36: 973. 1940.

The number of thrombocytes in the blood of normal menstruating women shows a phasic course. Since the peak of the thrombocyte curve coincides approximately with ovulation and the lowest point with menstruation, an endocrine regulation of this process is assumed. The number of thrombocytes is not appreciably influenced by the follicular hormone in physiological dosage but is diminished by the corpus luteum hormone. This action may perhaps serve as a test for preparations with suspected corpus luteum hormone properties.—*Ruth Berggren (courtesy Chem. Abstracts).*

CORNER, G. W.

The rate of secretion of estrogenic hormones by the ovaries of the monkey, *Macaca rhesus*. *Arch. Internat. de pharmacodyn. et de thérap.* 66: 79. 1941.

A tentative estimate of 0.02 mg. per day of estrone by a 4 to 5 kg. monkey is made. This is equivalent to about 0.3 mg. per day for a human female. Clinical trials indicate secretion of about 0.42 mg. per day in human females.—*G.A.E. (courtesy Biol. Abstracts).*

COUNCELLER, V. S.

Ten years' experience in the management of cryptorchidism. *J. Urol.* 46: 722. 1941.

This paper deals largely with surgical methods. The author concludes "Hormonal therapy in cryptorchidism should be confined to a relatively few patients and then only if spontaneous descent seems improbable. It may be used with benefit in cases of hermaphroditism or hypogonadism."—*Author's conclusions. J.C.D.*

CURTIS, A. H.

Theca cell tumors (thecoma). *Surg., Gynec. & Obst.* 73: 481. 1941.

Well-illustrated operative material containing a 'high amount of estrogen per gram of tissue' was obtained from a 52-year-old female who was still menstruating freely. Report is of interest in view of the conception that the theca and not the granulosa cells are the source of ovarian estrogens.—*A.T.K.*

DIBLE, J. H., AND C. M. WEST.

A human ovum at the previllous stage. *J. Anat.* 75: 269. 1941.

Presumably the youngest human ovum recovered to date is described. Measurements included embryonic disc 0.1 by 0.02 mm., endodermal plate 0.14 by 0.016 mm., and amniotic cavity 0.04 by 0.09 mm.—*H.O.H.*

FRANK, R. T.

Diagnostic procedures in female sex endocrine problems. *Univ. Penna. Bicentennial Conf. Female Sex Hormones.* 1941. 33.

The concentration of estrogenic hormones in the blood, except during pregnancy is 0.1 to 50; hence determination

must be made by bioassay. By determination of gonadotropic activity of the blood and urine, a balance between secretion and excretion may be obtained. Estrogens occur in the urine in both free and combined forms; only free estrogens have been found in the blood. Androgens have not been found in 40-cc. samples of blood; their bioassay in urine is performed by determination of the growth response after application to the comb of a 3-day chick. The bioassay findings in the following conditions are reviewed: normal menstrual cycle, amenorrhea, menorrhagia, menopause, ovarian tumors, pregnancy, hydatid mole and chorio-epithelioma and adrenal cortical carcinoma. Estrogen increases progressively in the blood from the 8th week of pregnancy until its termination, but drops to zero within 24 hours after fetal death.—*J. S. Hepburn (courtesy Chem. Abstracts).*

FOLLEY, S. J.

Effect of estrogens on lactation. *Lancet* 1: 40. 1941.

In addition to inhibitory effects on lactation, estrogens will exert a galactopoietic action, as reflected in increase in concentration of both fatty and non-fatty solids in the milk. This galactopoietic action is characterized by a lower threshold than that for inhibitory action. Hence small doses enrich milk, whereas larger doses inhibit its secretion. Dissociation of the two effects is more readily obtained with the natural estrogens than with diethylstilbestrol.—*H.O.H.*

GALANG, CECILIA T.

Preliminary studies on the menstrual cycle of Filipino women students. *Acta med. Philippina* 2: 325. 1941.

Data on age at menarche and the influence of several factors on the menstrual cycle were obtained for 446 girls between the ages of 10 and 17 years enrolled in the Physical Education classes in the University of the Philippines. In 21.55% the onset of menstruation occurred at the age of 12 years; in 34.47% at 13; and in 26.50% at 14. There appeared to be no differences in age at menarche which could be attributed to climate, but the samples on which the figures were based were small: 35.71% of the 112 students on whom the effects of indulgence in physical exercise were studied noticed no effect on their menstruation; 23.21% had increased flow; 14.28% had cessation of menses; 10.71% had the onset of succeeding menses hastened; 11.60% had the onset delayed; and 4.46% experienced diminished flow. Physical exercise was therefore concluded to have a variable influence on individuals, 'personal adaptation' being the controlling factor.—*Courtesy Child Development Abstracts.*

GRAY, L. A.

Progesterone in nervous tension states. *South. M. J.* 34: 1004. 1941.

"A series of 38 women with nervous tension states, probably of endocrine and psychiatric etiology, is reported. Relief of symptoms with no formal psychotherapy occurred in the majority of cases after intramuscular injections of progesterone."—*Author's summary. J.C.D.*

GREENBLATT, R. G.

Histologic changes in the ovary following gonadotropin administration. *Am. J. Obst. & Gynec.* 42: 983. 1941.

The author substantiates his previous finding that the use of gonadotropins, of various sources, fails to invoke an orderly process of maturation, ovulation, and corpus luteum formation in patients with primary ovarian insufficiency. The hope is expressed, however, that ultimately proper dosage, timing and optimal hormone combination will lead to more promising results. The report is based upon 36 cases in which examination of the results of gonadotropin administration was made incidental to laparotomy.—*H.O.H.*

HALBERSTAEDTER, L.

The role of artificial menopause in the treatment of cancer of the breast. *J. Internat. Coll. Surgeons* 4: 435. 1941.

In defense of oöphorectomy as an auxiliary measure in treatment of mammary carcinoma, the author cites earlier clinical observations and more recent experimental work. Two cases are reported in which roentgen-ray or surgical castration appeared to have been of definite value.—*H.O.H.*

HEARD, R. D. H., AND M. M. HOFFMAN.

Steroids. IV. The fate in man of injected α-estradiol. *J. Biol. Chem.* 141: 329. 1941.

A total of 250 mg. of purified α-estradiol was administered intramuscularly to a normal male subject in order to ascertain the nature of the urinary excretion products. Recovered unchanged were 9.8 mg. (3.9%), while oxidized to estrone (isolated as such) were 16.2 mg. (6.4%). No estriol or β-estradiol was obtained. Thorough exploration of the urine by systematic fractionation and chromatographic analysis failed to separate any other compounds which could be recognized as estrogen metabolites. Isolated were the usual steroids of normal male urine, androsterone, dehydroisoandrosterone, etiocholan-3 (a)-ol-17 one, pregnane-3(a)-20(a)-diol, and cholesterol, together with very small quantities of 3 unidentified substances. The fate of the remaining 90 per cent of the hormone, inactivated in the body, is discussed.—*Authors' summary.*

HECKEL, N. J., AND C. R. STEINMETZ.

The effect of female sex hormone on the function of the human testis. *J. Urol.* 46: 319. 1941.

Three patients, aged 60, 69 and 72, were treated for prostatic symptoms with estradiol benzoate. They received totals of 1,400,000; 1,200,000 and 1,600,000 R.U. in 31½, 45 and 28 weeks. The spermatozoa count fell from about 1,000; 820 and 720 millions to zero. There was temporary stimulation of the breast tissue and loss of libido.—*J.C.D.*

HOWARD, J. E.

Chemical, physiological and clinical aspects of the androgens. *Bull. New York Acad. Med.* 17: 519. 1941.

A review of the appreciation of the physiology of the androgens in their application clinically to the human male is presented.—*C. T. Kaylor (courtesy Biol. Abstracts).*

JOHNSON, W. O.

Limitations of estrogen therapy. *South. M. J.* 30: 1006. 1941.

In understanding the limitations of estrogen therapy and using these products properly, correct diagnosis and specific therapy given to individuals in the best possible state of health is essential. Some of the conditions treated by estrogen therapy, in which results have not been wholly satisfactory, have been reviewed and an appeal has been made to use organotherapy only as a specific therapy.—*Author's abstract.*

KEARNS, W. M.

Testicular transplantation. Successful autoplastic graft following accidental castration. *Ann. Surg.*, 114: 886. 1941.

Satisfactory results were obtained through scrotal autoimplantation of testis slices in a 23-year-old patient. Criteria of functional activity were based upon prostatic gland maintenance and secretion, persistence of libido and of normal clinical and laboratory tests.—*H.O.H.*

KUNSTADTER, R. H.

The hormone treatment of cryptorchidism: eight years' experience. *Urol. & Cutan. Rev.* 45: 81. 1941.

In 8 years, 71 cryptorchids were treated by hypodermic administration of either chorionic or equine gonadotropin. Sixty-five patients had previously received no form of therapy. Six had previously been subjected to surgery. In the former group, complete descent occurred in 45 (69.2%) partial descent in 7 (10.8%) and complete failure occurred in 13 (20%). Eighteen (27.7%) were unilateral and 47 (72.3%) were bilateral. Twenty-seven (41.5%) were of a a normal constitution, and 38 (58.5%) showed definite evidence of an endocrine disturbance. A definite correlation between endocrine dysfunction, bilateral cryptorchidism and successful hormone therapy was observed. The majority of failures occurred in unilateral cryptorchids of a normal constitution. Six patients received hormone therapy following unsuccessful surgery and this proved to be of value in 3 patients. Response to hormone therapy usually occurred with a total dose of 2,500 to 7,200 R.U. of chorionic gonadotropin and from 240 to 2,550 units of equine gonadotropin. A large percentage of testes undescended at puberty are sterile. Many patients present endocrine disorders that may not improve spontaneously. Some have psycho-sexual disturbances. It is suggested, therefore, that all boys with cryptorchidism should receive endocrine therapy between 8 and 12 years of age. The parents of all patients treated should be informed that in the event of unsuccessful treatment, surgical correction should not be delayed.—*Courtesy Clin. Abstracts.*

LESSER, M. A.

The treatment of angina pectoris with testosterone propionate. *New England M. J.* 226: 51. 1942.

On the basis of the reported circulatory effects of testosterone proprionate, the author was led to its use in the management of angina pectoris. Favorable results were obtained in 24 patients who received 25 mg. intramuscularly every 2nd to 5th day. The response on the part of 20 males appeared definitely more pronounced than in the 4 females.—*H.O.H.*

LIN, H. A. C.

Treatment of gonococcal vulvo-vaginitis by estrogenic suppositories. *Chinese M. J.* 58: 527. 1940.

Daily doses of 100 to 150 R.U. of the estrogens from pregnancy urine for 10 to 50 days gave satisfactory results.—*B.C.P.A.*

LOFTIS, E.

Purpura due to injection of estrogenic substances. *Arch. Dermat. & Syph.* 42: 138. 1940.

A case of purpura localized to the buttocks and thighs is presented. The etiologic agent was an estrogenic hormone which was being administered intramuscularly. On cessation of the administration of this substance the purpura disappeared.—(*courtesy Allergy Abstracts*).

MACBRYDE, C. M., D. CASTRODALE, ELLEN LOEFFEL AND H. FREEDMAN.

The synthetic estrogen diethylstilbestrol—clinical and experimental studies (II). *J.A.M.A.* 117: 1240. 1941.

In a series of 202 estrogen-deficient cases, the authors found that diethylstilbestrol therapy gave subjective and objective relief in 85%. Poor results were obtained in 4%. They advise intermittent rather than continuous treatment and find that 0.3 to 0.5 mgm. daily for 2 to 3 weeks each month is frequently sufficient. Liver function, blood and urine studies gave essentially normal results. On continuous treatment nausea occurred in 20% of the cases, but on intermittent treatment the incidence was only 8.6%.—*C.P.*

MARKHAM, M. J.

The clinical use of testosterone propionate in benign prostatic hypertrophy. *Urol. & Cutan. Rev.* 45: 35. 1941.

In 7 cases testosterone propionate produced moderate to marked relief of all the symptoms of prostatism. Testosterone propionate is definitely indicated in the treatment of the symptoms of benign hypertrophy of the prostate: (a) where operation involves a definite risk to the patient's life; (b) where the palliative operation of transurethral prostatectomy has been unsuccessful; (c) in mild cases where surgery is not urgent and the patient is completely unwilling to submit to any form of surgery.—*Courtesy Clin. Abstracts.*

MCCULLAGH, E. P., AND R. JONES.

A note on the effect of certain androgens upon the red blood cell count and upon the glucose tolerance. *Cleveland Clin. Quart.* 8: 79. 1941.

Long continued androgen therapy in a case of eu-

nuchoidism resulted in a rise of 25% in B.M.R. during course of treatment, an increase in red cell count (4.16 pre-treatment level to a high of 5.64), with increase in Hb. and hematocrit. Decreased glucose tolerance has also been noted in similar cases. These effects subsided upon withdrawal of treatment.—*H.O.H.*

MENDEL, E. B., A. M. GOLDMAN AND A. CAIRE, JR.

Inhibition of lactation with stilbestrol. *Am. J. Obst. & Gynec.* 42: 528. 1941.

Stilbestrol was used in 55 cases to inhibit or stop lactation both before and after lactation had occurred. In the average cases, a total of 20 mg. was used in the non-engorged and 30 mg. in the engorged or lactating breasts. The end results of both procedures were satisfactory. Abscess formation in the engorged breasts, as well as excessive amounts of fluid by the intravenous route and prolonged lactation, seemed to necessitate an additional amount of drug therapy. Three cases of severe painful engorgement of the breasts in the nursing mother responded favorably to 10 mg. stilbestrol without inhibiting lactation. In 1 case of severe juvenile diabetes the administration of stilbestrol did not affect the insulin requirement.—*Ruth Berggren (courtesy Chem. Abstracts).*

MOORE, R. A., M. L. MILLER AND A. MCLELLAN.

The urinary excretion of androgens by patients with benign hypertrophy of the prostate. *J. Urol.* 44: 727. 1940.

Critical study of the method showed that, in any given study, a procedure must be accurately standardized and rigidly followed. The important points are: complete acidification and hydrolysis of the urine within 24 hours; the use of boiling rather than autoclaving for hydrolysis; hydrolysis of the acidified urine in a constant volume; and extraction with at least 10 volumes of benzene. Each 3-day specimen was assayed by the colorimetric method of Oesting, using the Zimmerman m-dinitrobenzene reaction, and by bioassay in capons. With normal urine there is a satisfactory correlation of the 2 tests, but with urine from older men with disease of the prostate there is an evident increase of chromogenic substance which is not biologically active. The average, maximum, and minimum excretions of androgens, in the equivalents of I.U. androsterone per day, were: young men (20 to 35 years) 19.4, 25.3, 10.3; older men without benign hypertrophy, 9.0, 16.6, 6.1; older men with benign hypertrophy, 6.7, 15.3, 2.2. Interpretation of these findings must await further investigation.—*R. Berggren (Courtesy Chem. Abstracts).*

MOORE, R. A., M. L. MILLER AND A. MCLELLAN.

The chemical composition of prostatic secretion in relation to benign hypertrophy of the prostate. *J. Urol.* 46: 132. 1941.

Chemical analyses of the prostatic secretion in dogs and in man before and after the infection of an androgen and an estrogen lend no support to the theory that benign hypertrophy of the prostate is due to an excess of either hormone.—*Authors' conclusions.*

NATHANSON, I. T., R. B. MILLER, LOIS E. TOWNE AND J. C. AUB.

The close correlation of androgen and creatinine excretion in normal children. *Endocrinology* 28: 866. 1941.

In growing children of both sexes there is a close correlation between the excretion of the 17-ketosteroids and of creatinine. The correlation of these 2 substances is so close that it seems highly likely that there is a fundamental relationship between them. The most likely explanation appears to be that androgens have an influence on the muscle mass of the individual so that an increase in androgen formation would result in an increased muscle mass, and therefore an increase in the rate of creatinine excretion.—*F. Saunders (Courtesy Chem. Abstracts).*

NATHANSON, I. T., LOIS E. TOWNE AND J. C. AUB.

Normal excretion of sex hormones in childhood. *Endocrinology* 28: 851. 1941.

This study is based on 1100 determinations on 59 normal girls and 40 normal boys: 565 were for estrogen, 495 for 17-ketosteroids, and 40 for the follicle stimulating hormone of the pituitary gland. It was found that from ages 3 to 7 years both boys and girls excreted a small but constant amount of estrogen and 17-ketosteroids in the urine, no striking difference in the excretion rates becoming obvious until about the age of 9 or 10 years. About 1½ years before menarche, estrogen excretion became cyclic in girls and the intensity of these cycles gradually increased. There was no cycle in 17-ketosteroid excretion in either sex, but after 11 years of age boys had a higher excretion. It appears that sexual maturity of boys and menarche in girls marks the culmination of a gradual endocrine development which starts about 5 years before puberty and that about 1½ years before maturity an additional mechanism appears which leads to more rapid differentiation of sex characteristics and eventual complete metamorphosis.—*Courtesy Child Development Abstracts.*

PALMER, H. D., D. W. HASTINGS AND S. H. SHERMAN.

Therapy in involutional melancholia. *Am. J. Psychiat.* 97: 1086. 1941.

In 53 patients the endocrine changes of the climacteric seemed to be related to the onset of the psychosis in only 24%. Treatment of the group with stilbestrol had no detectable favorable effect upon the psychosis though in some cases amelioration of menopausal conditions was seen. In 10 cases of involutional melancholia in men relatively little benefit of the psychosis from testosterone was seen but some improvement occurred in 2 early cases. In 15 cases combined use of parathormone, NH_4Cl and Ca gluconate was without significant clinical effect on the psychosis. It was concluded that life-long restrictions of the personality and traits deeply rooted in the psychobiology of the individual are more significant than physiological factors in the etiology of involutional melancholia.—*R.G.H.*

PINCUS, G., AND W. H. PEARLMAN.

Steroid excretion in cancerous and non-cancerous persons. II. Urinary estrogens. *Cancer Research* 1: 970. 1941.

Samples of pooled urines from 2 sets each of cancerous and non-cancerous males and females revealed by bioassay—(1) higher estrogenic activity in urine of non-cancerous females, compared with that of cancerous female subjects, (2) lower estrogenic activity in the urine of non-cancerous males than in that of cancerous males, because of higher titers of non-ketonic fractions, (3) a higher 'estriol' fraction in urine of non-cancerous females than in comparable fractions of urine of cancerous females, (4) 'estradiol' fractions in the urine of cancerous males was higher than the corresponding fractions in non-cancerous males. Implications are discussed.—*H.O.H.*

SALMON, U. J., S. H. GEIST AND A. A. SALMON.

Effect of androgen administration upon pregnandiol excretion in cyclical women. *Proc. Soc. Exper. Biol. & Med.* 48: 11. 1941.

The effect of androgen administration upon pregnandiol excretion was studied in 8 women. The androgens used were: methyl testosterone (3 patients) orally, in daily doses of 50 to 100 mg. (total doses of 1480, 2350, and 2800 mg.); testosterone propionate in oil (3 patients) intramuscularly in individual doses varying from 50 to 100 mg. (total doses 600, 1050, 1175 mg.); and testosterone (500 mg.) and testosterone propionate (516.6 mg.) by pellet implantation (2 patients). Doses of androgens found in previous studies to be suppressive (i.e., to cause suppression of pituitary gonadotropic hormone excretion—inhibition of ovulation and menstruation) when administered early in the cycle, resulted in the absence of Na pregnandiol glucuronidate in the urine during the current cycle and led to suppression of the next expected menstrual period. In 1 patient 1175 mg. of testosterone propionate, administered after the 9th day of the cycle, did not appreciably affect the excretion of the pregnandiol complex during the current cycle.—*U. J. Salmon (courtesy Biol. Abstracts).*

SATTERTHWAITE, R. W., JUSTINA H. HILL AND ELIZABETH F. PACKARD.

Experimental and clinical evidence on the role of the 17-ketosteroids in prostatic carcinoma. *J. Urol.* 46: 1149. 1941.

The urinary 17-ketosteroids were determined for 15 patients with prostatic carcinoma, 10 of whom were subjected to bilateral orchidectomy. In these 10 clinical improvement was correlated with decrease in urinary titer. The average level in the 15 patients prior to therapy ranged from 2.3 to 12.6 mg. per 24-hour sample, which is within the normal range for elderly men without prostatic disease. Maximal clinical improvement was obtained in 2 patients who post-orchidectomy had the largest drop in 17-ketosteroid titer, i.e., relief of pain, decrease in urinary obstructive symptoms, and drop in basic phosphatase to normal levels. The patient showing least clinical improvement showed the least change in 17-ketosteroid value, an average reduction from 3.9 to 3.4 mg. In the remaining 7 cases in which orchidectomy was performed, the clinical improvement appeared correlated with the per cent decrease in 17-ketosteroid titer.—*H.O.H.*

SAVITZ, S. A., AND S. CHARTOCK.

The clinical application of an extract obtained from the animal prostate gland. *Med. Rec.* 152: 3. 1940.

Treatment of 20 patients suffering from chronic prostatitis with an isotonic extract of fresh beef prostate elicited sufficient response to encourage consideration of this substance as a therapeutic agent.—*H.O.H.*

SCHOCKAERT, J. A., G. DELRUE AND J. FERIN.

Comparative activity of estradiol and dioxy-di-ethyl-stilbene on vaginal pH in women. *Compt. rend. Soc. de biol.* 131: 1309. 1939.

By a vaginal pH test stilbestrol given orally or parenterally proved neither so potent nor so uniformly effective as estradiol benzoate administered intrasmuscularly.—*E. Cutuly.*

SCHOCKAERT, J. A., AND J. FERIN.

Endometrial changes induced in ovariectomized women by feeding estrogens. *Acta brev. Neerland.* 11: 184. 1941.

Castrate urine induces follicle ripening without luteinization in the immature mouse. In the hypophysectomized mouse, castrate urine and pregnyl (P.U.) together cause luteinization and follicle ripening. Luteinization is therefore the result of the activity of two substances, one stimulating the follicles and the other the development of the interstitial cells. Analogous effects with these two substances are observed in the testicle.—*M. L. C. Bernheim (courtesy Chem. Abstracts).*

SHUTE, E.

Hormone management of the nausea and vomiting of early pregnancy. *Am. J. Obst. & Gynec.* 42: 490. 1941.

Thirty-five patients with vomiting in early pregnancy, who had high blood estrogenic levels, received testosterone propionate 10 mg. q. 3 d.; 80% were 'cured' and 14% 'greatly helped.' Fifteen similar patients with low blood estrogens were treated with estrogens 10,000 I.U. q. 3 d.; 73% were 'cured' and 20% 'much helped.'—*E.C.H.*

SMITH, R. E.

The undescended testicle. *Lancet* 747. 1941.

Undescended testicles associated with clinical heriae should be treated surgically; others should be given the chance to descend spontaneously at puberty. If they fail to do so operation should be performed without delay. A preliminary course of hormone therapy will not often cause descent, but will make operation easier. Under this treatment the testicle undoubtedly hypertrophies, as can be judged clinically, and coincident with this is an increase of the circulation, fragile spermatic blood-vessels becoming able to withstand the strain of being stretched when the testicle is inserted into the scrotum. Usually one post-

operative course of hormone therapy will cause the testicle to enlarge further and maintain its new position. Puberty is the ideal age for operation, for at this time there is an excess of gonadotropic substances in circulation. Most of the testicles which do not descend spontaneously will be found to be ectopic or to have anatomical obstructions.—*Courtesy Clin. Abstracts.*

SOULE, S. D.

Anhydro-hydroxy-progesterone in threatened abortion. *Am. J. Obst. & Gynec.* 42: 1009. 1941.

Sixteen of 20 cases of threatened abortion were maintained to term by oral anhydro-hydroxy-progesterone, in dosages up to 100 mg. per day, and hypodermic progesterone, 1 to 30 mg. per day. No toxic symptoms were noted. Of the 8 multiparae carried through, 5 had aborted at least once previously.—*H.O.H.*

SPENCE, A. W.

Preparations of testosterone in eunuchism and hypogonadism. *Quart. J. Med.* 9: 309. 1940.

The effectiveness of the preparations was demonstrated on 2 eunuchs and 4 patients by intramuscular injections of testosterone propionate, implantation of tablets, inunction of testosterone and of testosterone propionate as an ointment or tincture, and oral administration of methyl testosterone. Potency was established and secondary sexual characteristics developed. In several cases psychological disturbances disappeared; there were improved mental outlook and pugnacity, increased libido, muscular strength and growth of testes and prostate. The effectiveness of each preparation was demonstrated. The maintenance doses required to produce about a similar effect were: (1) testosterone propionate intramuscularly, 50 to 75 mg. per week, given in 2 or 3 injections, (2) daily inunction of testosterone propionate as an ointment, 32 to 49 mg. per week, (3) daily inunction of testosterone as an ointment, 17.5 mg. per week, (4) oral administration of methyl testosterone, 350 mg. per week in doses of 10 mg. 5 times a day. Free testosterone implanted as a 50 mg. tablet exerted its action for 8 to 10 weeks.—*B. C. Russum (Courtesy Biol. Abstracts).*

SPURT, H.

Cyclic changes in the mammary gland of the rhesus monkey. *Surg., Gynec. & Obst.* 73: 388. 1941.

The difficulties surrounding attempts to determine the nature of the human mammary cycle from biopsy specimens of diseased breasts and from autopsy material are cited. Whole mounts of the breasts of rhesus monkeys supplemented by histological study reveal premenstrual enlargement of the lobules with increased vascular engorgement occurring only in ovulatory cycles.—*A.T.K.*

TEAGUE, R. S.

The effect of estrogens on the microscopic appearance of the liver. *J.A.M.A.* 117: 1242. 1941.

Teague finds that the vacuoles in livers from rats treated with diethylstilbestrol are predominantly glycogen when selectively stained. This deposition of glycogen is comparable to that produced by other estrogens, and hence he concludes that the synthetic substitutes do not produce a serious toxic effect on the liver.—*C.P.*

TWOMBLY, G. W., AND A. F. HOCKER.

Chorioepithemioma in the male, treated with pregnancy serum. *Surg., Gynec. & Obst.* 73: 753. 1941.

Chorioepithelioma of the testis of a 33-year-old male was carefully studied by endocrine assay and at autopsy. The pituitary gland showed an increase in basophil cells and degranulation of eosinophils characteristic of pregnancy with absence of gonadotropic material in the acetone-dried gland. Gonadotropic material on the order of 40,000 to 130,000 mouse units (M.U.) was excreted per day, increased to 440,000 M.U. per day by treatment with serum of pregnant women. Seventy-two hour urine specimens contained 533 to 1110 M.U. estrone, 11 to 90 M.U. estradiol, 60 to 80 M.U. estriol (methods of Smith and Smith). These quantities, higher than those of normal males are sufficient to explain the patient's gynecomastia. Seventy-two hours specimens gave 20 to 24 mg. androsterone equivalents per day (colorimetric method of Callow, Callow and Emmens), 3.1 mg. androsterone equivalents per day (chick comb after Dorfman). These are normal values. Two 48-hour specimens showed 11 to 16 m. of crystalline material probably free pregnandiol (Venning).—*A.T.K.*

WALTER, R. I., U. J. SALMON AND S. H. GEIST.

Amenorrhea due to tuberculous endometritis. Failure of estrogens and progesterone to induce uterine bleeding. *Am. J. Obst. & Gynec.* 42: 505. 1941.

A case is reported wherein a patient, aged 23 years, who was treated with 1,028,000 R.U. of α estradiol benzoate given intramuscularly in oil, 860,400 R.U. of α estradiol given orally and 120 mg. of progesterone, over a period of 14 months, failed to experience uterine bleeding. Suction curettage after therapy disclosed the existence of atrophy of the endometrium and tuberculous endometritis.—*E.C.H.*

V. WESSELY, F.

Synthetic estrogens. *Angew. Chem.* 53: 197. 1940.

A critical review of the synthetic estrogens, particularly the stilbestrols, of animal experimentation and therapeutic use. Sixty-one references.—*W. F. Bruce (courtesy Biol. Abstracts).*

WIESBADER, H.

Oral therapy with pregneninolone in functional uterine bleeding. *Am. J. Obst. & Gynec.* 42: 1013. 1941.

In 20 cases of functional bleeding, oral pregneninolone, in dosages up to 50 mg. per day, was well tolerated, with beneficial effects in 17 cases. In the 3 unresponsive cases (juvenile bleeding) 25 to 50 I.U. progesterone by injection stopped bleeding within 72 hours. Regular cycles were re-established upon suitable reduction of medication. Total effective dosages of pregneninolone ranged from 280 to 350 mg. in 50 mg. daily doses.—*H.O.H.*

WILKINS, L., W. FLEISCHMANN AND J. E. HOWARD.

Creatinuria induced by methyl testosterone in the treatment of dwarfed boys and girls. *Bull. Johns Hopkins Hosp.* 69: 493. 1941.

In 7 cases of dwarfism treated with methyl testosterone, 25 mg. per day orally, N retention appeared within the first 3 days of treatment, and increased creatinuria within 10 days. This increase continued and reached a high level by the 2nd to the 5th month. Withdrawal of treatment resulted in prompt N equilibrium or deficit, with gradual decrease in creatinuria over a 16 to 26 day period.—*H.O.H.*

HYPOPHYSIS

BICKERS, W.

Shock from posterior pituitary extract. *South. M. J.* 34: 112. 1941.

Shock from this cause is rare but its recognition is important since it yields quickly to adrenalin, while the ordinary post partum shock due to hemorrhage requires a transfusion. A case in which this type of shock occurred at the close of two successive pregnancies is reported.—*J.C.D.*

CONLEY, R. M.

Adamantinoma of the craniopharyngeal duct. *Am. J. Dis. Child.* 61: 6. 1941.

The case of a 6½ year old girl with an adamantinoma of the craniopharyngeal duct with resultant manifestations of marked cachexia and Levi-Lorain type of pituitary infantilism is reported. Microscopic examination of the pituitary showed invasion of the posterior lobe by tumor tissue. The anterior lobe was compressed. Medical treatment is of no avail in cases of dwarfism or adiposity caused by tumors in this area. The operative mortality is high. The literature, diagnosis and treeatment are discussed in detail.—*M.B.G.*

EVANS, H. M.

Growth hormone of the anterior lobe of the pituitary gland. *J.A.M.A.* 117: 287. 1941.

Growth hormone of anterior pituitary is discussed under the following headings: 1. Tests for regulation of growth by hypophysis. 2. Discussion of bioassay methods. 3. Growth-promoting preparations. 4. Metabolic effects of growth hormone. 5. Relation of anterior pituitary growth hormone to other hormones. 6. Clinical use of extracts containing growth producing substance.—*C.P.*

FARR, L. E.

Minimal nitrogen requirements of children with the nephrotic syndrome. Effect of the administration of a growth-promoting anterior pituitary extract. *Am. J. Dis. Child.* 60: 1324. 1941.

The administration of a growth-promoting extract of the anterior pituitary had no effect on the N assimilation of 3 nephrotic children. Intramuscular injection caused local reactions not observed when the same extract was given to other types of children.—*M.B.G.*

FERGUSON, J. K. W.

A study of the motility of the intact uterus at term. *Surg. Gynec. & Obst.* 73. 359. 1941.

Ferguson confirms the previous studies of Haterius and Ferguson to the effect that electrical stimulation of the pituitary stalk of the post-partum cat or rabbit induces contractions of the uterus. This occurs when neck tissue is crushed leaving only carotid and jugular connections between head and trunk intact. This is interpreted as due to the liberation of an oxytocic hormone from the posterior lobe. Although slight elevations in blood pressure occur, there is no evidence that these are responsible for the observed changes. Evidence is presented that dilatation of the uterine horn and cervix evoke oxytocin secretion reflexly and that dilatation of the vagina only occasionally does so but more consistently induces complex reflexes serving to delay uterine evacuation while the vagina is occupied.—*A.T.K.*

FINLAY, J., AND M. MAGIDAY.

Blood sugar in a case of complete hypophysectomy. *Arch. Int. Med.* 68: 893. 1941.

The total removal of the hypophysis in a 33-year-old male produced a drop in the fasting blood sugar to hypoglycemic levels. No shock accompanied these low values. Sugar tolerance curves were somewhat erratic, with a tendency to a delayed rise and, at times, a plateau. The level of the blood sugar was not wholly dependent on the pituitary gland. The pituitary gland functions as a blood sugar level-raising mechanism. The pituitary gland is not a vital organ.—*I. B.*

FRASER, R., AND PATRICIA H. SMITH.

Simmonds' disease or panhypopituitarism (anterior). Its clinical diagnosis by the combined use of two objective tests. *Quart. J. Med.* 10: 297. 1941.

The insulin tolerance test in 10 cases of suspected Simmonds' disease revealed a normal initial fall but a protracted recovery of blood sugar level. Myxedematous patients, on the other hand, showed a slow initial fall (insulin resistance). Urinary 17-ketosteroid assays proved essentially negative; 4 cases of anorexia nervosa gave positive values. Combined use of the tests will differentiate panhypopituitarism from allied syndromes. Insulin tolerance distinguishes primary myxedema; anorexia nervosa is differentiated by a positive 17-ketosteroid assay.—*H.O.H.*

FREUD, J., AND E. DINGEMANSE.

Augmentors for certain pituitary gonadotropins. *Acta brev. Neerland.* 11: 37. 1941.

There are 5 groups of augmentors for pituitary gonadotropins: (1) the chorionic gonadotropin of pregnancy urine, (2) the sulfates of Zn, Cu, Fe and Na, also $ZnCl_2$ and K soaps, (3) mucilaginous substances such as agar-agar, tragacanth, gum arabic and glycogen, (4) the Na salts of the bile acids and (5) gelding pituitary extract. Each augmentor can increase, at least 5 times, the gonadotropic effect of pituitary extract in young rats.—*M. L. C. Bernheim (courtesy Chem. Abstracts).*

GERNES, L.

Amounts of serum of gonadotropic hormone in normal and pathological pregnancy. *Compt. rend. Soc. de biol.* 132: 111. 1939.

Numerous studies on the serum level of gonadotropic hormone were made in cases of fetal retention after death, pernicious vomiting of pregnancy, mole, and various stages of normal pregnancy. The values were quite variable and there was considerable overlapping.—*E. Cutuly.*

GREENBLATT, R. B., AND E. R. PUND.

The Gonadotropine: A clinical and experimental study. With observations on the use of a new gonadotropic mixture and on combined equine and chorionic gonadotropin administration. *South. M. J.* 34: 730. 1941.

Eight cases of functional amenorrhea received gonadotropin therapy. The results were assayed through clinical observation and endometrial biopsies. When menstrual bleeding occurred it was usually from an estrogenic endometrium. In 7 bitches, known to be in anestrous, receiving gonadotropins, 2 came definitely into heat and the rest showed some signs of active estrous. From the above series and other observations, the authors conclude in part "Evidence is presented that makes it difficult to believe that in functional or primary amenorrhea the gonadotropins can stimulate the subthreshold ovary to ovulation and corpus luteum formation in spite of the clinical improvement of the patient. . . . The presence of pregnandiol glucuronide in the urine following gonadotropin medication, at a time when none is expected, and the appearance of false progestinal responses of the endometrium do not indicate ovulation and corpus luteum formation, but probably reflect the luteinization of atretic follicles or corpora atretica of the ovary as the result of medication." The work on bitches "leads one to believe that the gonadotropins can stimulate the normal ovary, at least in normal bitches, during the non-receptive stage. A new gonadotropic mixture containing a synergistic factor from the anterior pituitary and chorionic gonadotropin evoked responses in the normal human ovary similar to those obtained following pregnant mares serum or extract of the anterior pituitary. Bleeding could be induced with more regularity following combined administration of equine and chorionic gonadotropins than when either were administered alone, but bleeding, except in rare instances, occurred from an estrogenic endometrium." —*J.C.D.*

PASQUALINI, R. Q., AND E. ETALA.

The hypophysis and NaCl excretion *Rev. Soc. argent. de biol.* 17: 198. 1941.

The effect of pitressin on diuresis and NaCl excretion was studied in 14 normal subjects. Excretion of NaCl varied in the same sense as the excretion of water; it was not influenced by pitressin. In 2 cases of diabetes insipidus no relation was seen between the excretion of NaCl, polyuria and injection of pitressin. The fact that water is reabsorbed by the renal tubule before NaCl, which is only reabsorbed in the distal part of Henle's loop, serves to explain the regulation of the water and salt metabolism. —*J. T. Lewis.*

SELYE, H.

Effect of hypophysectomy on morphological appearance of kidney and on renotropic action of steroid hormones. *J. Urol.* 46: 110. 1941.

Female albino rats in groups of 6 or more were used, with similar groups as normal and operated controls. Progesterone desoxycorticosterone, testosterone, luteinizing hormone, follicle stimulating hormone, and the last two in association with testosterone were injected. They were given in quantities that were greater than that sufficient to give definite physiological effects on the sex organs. These hormones each had a growth stimulating effect on the kidney regardless of whether the animal was hypophysectomised or intact. In no case, however, were any of the hormones or their combinations used capable of completely overcoming the shrinkage of the kidney which follows hypophysectomy. The author concludes that the renotropic action of the steroids tested is not mediated through the hypophysis. The article contains a general review of the literature to date and 110 references.—*J.C.D.*

WADSWORTH, R. C., AND C. MCKEON.

Pathologic and mental alterations in a case of Simmonds' disease. *Arch. Neurol. & Psychiat.* 46: 277. 1941.

A case of Simmonds' disease is presented which appeared after childbirth and was associated early in the course of the illness with a manic-depressive psychosis. The pituitary gland showed a unique, progressive, nonspecific granulomatous process resembling allergic necrosis. There was secondary atrophy of the thyroid, adrenals, parathyroids, ovaries, uterus and breasts. These atrophic processes were accompanied by the development of marked cachexia and microsplanchnia. Scattered focal lesions observed in the central nervous system are attributed not to the psychosis but to the repeated attacks of hypoglycemia. Degenerative lesions in the supraoptic and paraventricular nuclei of the hypothalamus are thought to be secondary to destruction of the anterior lobe of the pituitary gland.—*Authors' summary* (*R.G.H.*)

PANCREAS

BARNES, C. A., T. D. CUTTLE AND G. G. DUNCAN

Histone zinc insulin—its pharmacologic characteristics and its application in the treatment of diabetes mellitus. *J. Pharmacol. & Exper. Therap.* 72: 331. 1941.

The comparative effects of identical doses of histone zinc, unmodified, crystalline, and protamine zinc insulin were observed under strictly controlled conditions in 12 diabetic patients and in 1 nondiabetic subject. The hypoglycemic effects of unmodified and crystalline insulin disappeared between 6 and 8 hours after administration, whereas those of histone zinc insulin subsided in 18 to 22

hours, and those of protamine zinc insulin between 24 and 36 hours. The blood sugar lowering effect of histone zinc insulin was less abrupt and more prolonged than that of unmodified and crystalline insulin but more prompt than that of protamine zinc insulin. These qualities make it possible to secure a continuously normal blood sugar level and a freedom from glycosuria in a larger number of patients after a single injection of histone zinc insulin than is possible when other preparations are employed.—*Author's summary.*

Barnes, C. A., T. D. Cuttle and G. G. Duncan.

Histone zinc insulin, its pharmacologic characteristics and its application in the treatment of diabetes mellitus. *J. Pharmacol.* 72: 331. 1941.

In human diabetics the hypoglycemic effects of unmodified and crystalline insulin disappeared in 6 to 8 hours after injection, the effects of equivalent doses of histone Zn insulin subsided in 18 to 24 hours, and those of protamine Zn insulin in 24 to 36 hours.—*L. E. Gilson (courtesy Chem. Abstracts).*

Bates, G., and C. Weiss.

Delayed development of antibody to staphylococcus toxin in diabetic children. *Am. J. Dis. Child.* 62: 346. 1941.

The development of antistaphylolysin was studied (α) in the serum of 14 normal children and the titers compared with those of a similar group of diabetic children. There was a delay in the development of antibody after intradermal injection of staphylococcus toxin in diabetic children. A correlation was observed between the state of diabetic control and the antistaphylolysin response of a group of diabetic patients. Diabetic children whose disease was excellently controlled responded in antibody production much as normal children whereas those whose diabetes was poorly controlled showed a definitely retarded and diminished production of antihemolysin.—*M.B.G.*

Chase, Lillian A.

Diabetes mellitus: problems of its control. *Canad. M. A. J.* 44: 250. 1941.

The mortality from diabetes increased in Canada from 12.1 in 1933 to 14 in 1937. The death rate is highest in Ontario and lowest in Saskatchewan. The author discusses the role of hereditary and constitutional factors in the pathogenesis of the disease and stresses the excellent clinical results obtained with protamine zinc insulin in combination with a suitable diet.—*H. Selye.*

Conn, J. W., and Elizabeth S. Conn.

Metabolism in hyperinsulinism. I. Quantitative studies of the variations in the rate of combustion of carbohydrate produced by alterations in the diet. *Arch. Int. Med.* 68: 876. 1941.

In organic hyperinsulinism an enormous overcombustion of carbohydrates signalizes an average diet of carbohydrate, fat, protein. The rate is restored to normal levels by extirpation of islet cell tumor. Low carbohydrate diet depresses the postabsorptive rate of carbohydrate oxidation to levels seen under similar intake in normal subjects. However, the blood sugar level falls to hypoglycemic levels. Such low carbohydrate feeding inhibits the rate of hepatic glycogenolysis. In all conditions studied excessive liberation of insulin seems to be involved.—*H.O.H.*

Conn, J. W., and Elizabeth S. Conn.

Metabolism in hyperinsulinism. II. Effects of epinephrine on glycemic level and on combustion of carbohydrate. *Arch. Int. Med.* 68: 1105. 1941.

In normal subjects and in those with organic hyperinsulinism the postabsorptive rate of carbohydrate combustion was not increased by dosages of epinephrine of sufficient magnitude to produce a prolonged hyperglycemia. The R.Q., if affected at all, was slightly depressed. Combustion of carbohydrate was not affected by the average height of blood sugar level, of itself. While epinephrine had little effect, ingested dextrose evoked excessively increased combustion, especially in cases of organic hyperinsulinism. From the results epinephrine would appear a valuable adjunct to treatment of severe organic hyperinsulinism, since its use does not increase sugar combustion while at the same time some relief is afforded the process of hepatic glycogenolysis.—*H.O.H.*

Conn, J. W., and Elizabeth S. Conn.

Metabolism in hyperinsulinism. III. Effects of adrenal cortical extract on blood sugar and on sodium and nitrogen metabolism. *Arch. Int. Med.* 68: 1115. 1941.

Daily administration of 30 cc. of adrenal cortical extract to a patient with organic hyperinsulinism produced no anti-insulin or blood sugar raising effects, although the potency of the material used was attested to by its influence on Na and N balance. The dosage level may be an important factor in the use of adrenal cortical substances in clinical work, since it is pointed out that on a weight basis, much larger dosages have been employed in animal experimentation.—*H.O.H.*

Daniel, W. A.

A study of insulin tolerance and glucose tolerance tests on normal infants. *J. Pediat.* 19: 789. 1941.

Fasting blood sugar levels in a series of infants 2 to 22 months old revealed values of 52 to 95 mg.%, average 71.5, based upon 37 determinations. Insulin tolerance and glucose tolerance tests on 25 and on 12 subjects respectively demonstrated that while the former is a safe method, the low blood sugar values obtained render its value somewhat equivocal as a diagnostic aid. The considerable variations found in the glucose tolerance test give it a dubious significance when used on subjects under 2 years of age.—*H.O.H.*

Daugherty, J. A.

Endocrine manifestations in diabetic patients. *Pennsylvania M. J.* 45: 229. 1941.

The case histories of 425 diabetics were studied to determine the incidence of endocrine disturbance. Only

case of hyperfunction of the pituitary body was seen in this series of cases. The diabetes was of severe type. In all cases of pituitary hypofunction, the diabetes was severe. This is entirely contrary to experimental diabetes in which hypofunction produces a mild form of diabetes. Hyperthyroidism occurring during the course of diabetes showed an increase in the severity of the diabetes and difficulty in control. Hypoglycemic reactions and acidosis occurred frequently. Cure of hyperthyroidism produces a stable diabetic state. There must be some disturbance of glycogen storage and metabolism in hyperthyroidism which would correlate the physiologist's point of view. However, in several cases where diabetes followed the occurrence of hyperthyroidism the diabetes was not a very severe type. Hyperthyroidism cannot be given as a very prevalent cause of diabetes mellitus. Hypothyroidism should therefore ameliorate the diabetic state, but the cases herein reported showed the opposite to be true. Thyroid extract helped to permit the control of diabetes with diet and insulin. Gonadal disturbances in the female definitely affect the course of diabetes. Hypofunction certainly seems to aggravate the diabetic state. The effect of endocrine disturbances on the diabetic state, as seen clinically, is similar to the effect of the state of nutrition, the level of the metabolic rate, body temperature, exercise, infections, and a multitude of other variables. The primary abnormality in diabetes mellitus is in the insular mechanism.—*I. B.*

EDITORIAL.

The insulin monopoly. *J.A.M.A.* 117: 112. 1941.

This editorial reviews the history of the patent rights to insulin and discusses the action of the government in bringing suit against the 3 United States manufacturers under the Sherman Anti-trust Act.—*C.P.*

GRIFFITHS, M.

The antagonism between insulin and posterior lobe pituitary extract. *J. Physiol.* 100: 112. 1941.

No satisfactory answer can yet be given to the question of the existence of a direct antagonism between insulin and posterior lobe extract.—*E. D. Walter (courtesy Chem. Abstracts).*

JACKSON, R. L., AND I. BARTH.

Effect of adding vitamin B complex to the diets of stabilized diabetic children. *Am. J. Dis. Child.* 62: 516. 1941.

This study was undertaken in 5 diabetic children to determine if addition of vitamin B complex to standard diets for diabetic patients would alter the insulin requirement. Thiamin, 2 to 3 mg. in the form of vitamin B complex was added to the daily diet with an adequate supply of insulin and blood sugar levels were studied. Two of the patients were then watched for 2 weeks without additional vitamin B. The ingestion of vitamin B complex in excess of the amounts obtainable in well planned diets did not change the insulin requirements of well controlled diabetic patients.—*M.B.G.*

LEE, R. H.

The ocular fundus in diabetes mellitus. *Arch. Ophth.* 26: 181. 1941.

No changes were found in the fundus of patients below the age of 40. In one group every patient with marked retinal disturbance had, in addition to different degrees of sclerosis, some abnormalities of blood pressure, and in every case except 2 the E.K.G. showed myocardial degeneration. In patients beyond the age of 50 it is rare not to find retinal lesions of diabetes, and these were typical in 6 cases. In the majority of these the E.K.G. revealed pathologic change. In another group the E.K.G. revealed in almost every case pathologic changes in the heart and vascular system. However, the cases were evenly divided as to retinal changes. Sclerosis and hypertension were evident in every case. In 5 there were typical retinal lesions of diabetes. No changes in the fundus were found in 69% of the cases. Metabolic disturbance alone does not seem responsible for the retinal changes. In the majority of instances of diabetic retinitis there was associated arteriosclerosis, hypertension, nephritis or a combination of these, frequently combined with myocardial degeneration.—*R. H. Lee.*

LOEB, R. F.

The practitioner and problems of diabetes. *California & West. Med.* 55: 182. 1941.

When overnutrition is abolished in a community, the incidence of diabetes is decreased, and this suggests a possible relationship between exhaustion of insulin supply and diabetes.—*M. L. Ilsley (courtesy Chem. Abstracts).*

MASON, H. H., AND D. H. ANDERSEN.

Glycogen disease. *Am. J. Dis. Child.* 61: 795. 1941.

Five groups are listed: *a)* Glycogen storage disease of the liver (true Von Gierke's disease) due to a defect, probably congenital, in 1 portion of the enzyme system which performs the conversion of glycogen to dextrose and dextrose to glycogen. *b)* Glycogen storage disease of the heart and muscles. The defect is present in another part of the enzyme system. *c)* Cases associated with galactosuria—probably due to a defect in the enzyme system of the liver that converts galactose to glycogen. *d)* The excess deposition of glycogen is due to the secretion or administration of excessive amounts of insulin and the ingestion of large amounts of carbohydrate. *e)* Miscellaneous group. A case is reported with clinical and postmortem studies which place it in the 1st group.—*M.B.G.*

MAURIAC, P., L. SERVANTIE AND A. BARON.

Demonstration of hyperlipemia induced in diabetics. *Compt. rend. Soc. de biol.* 132: 145. 1939.

Micro-determinations were made in 6 diabetic cases to determine the extent of lipemia following a standard procedure of fasting and fat ingestion. The patients fell into 3 classifications: *a)* Negligible or no hyperlipemia due to faulty absorption, accompanied by a low fasting lipemia; *b)* Hyperlipemia and normal lipemia in individuals without

faulty nutrition; c) Normal or augmented fasting lipemia, or hyperlipemia always exaggerated, indicating decreased fat tolerance, occurring in grave conditions of diabetes.—*E. Cutuly.*

MEYER, K. A., L. AMTMAN AND L. PERLMAN.

Islet cell tumors of the pancreas. *J.A.M.A.* 117: 16. 1941.

A comprehensive review of the literature on islet tumors is given. The criteria for differentiation between the organic type of hyperinsulinism and the functional type are discussed, and it is pointed out that tumors are not under nervous or hormone control and are continually secreting insulin. A complete case report with successful removal of the tumor is reported.—*C.P.*

NELSON, W. E.

Diabetic children in non-diabetic camp. *J. Pediat.* 19: 25. 1941.

Diabetic children receiving adequate medical treatment can be normally active and can be permitted to partake of physical activity within ordinary limits. When special camps for diabetic children are not available, such children may be admitted to established camps which have adequate health supervision.—*M.B.G.*

SOSKIN, S.

The blood sugar: its origin, regulation and utilization. *Physiol. Rev.* 21: 140. 1941.

This is a review article with a summary on the mode of action of insulin. Some of the subjects covered in the discussion are site of formation, gluconeogenesis from protein and fat, homeostatic mechanism in the liver, pancreas, anterior hypophysis, thyroid, adrenal cortex, and other factors in regulation and emergency mechanisms, significance of utilization versus oxidation, significance of the R.Q. as judged from determination in vitro on isolated tissues and attempts to measure carbohydrate utilization in intact and liverless animals.—*H. R. Getz (courtesy Chem. Abstracts).*

STADIE, W. C.

Fat metabolism in diabetes mellitus. *Ann. Int. Med.* 15: 783. 1941.

Study of liver slices from diabetic cats showed abundant formation of ketones but neither the acetic acid nor sufficient O_2 uptake predicted from the Knoop B-oxidation hypothesis. The fatty acids oxidized all appeared as ketones. The multiple alternate oxidation hypothesis is in accord with the facts. The O_2 uptake is accounted for by deamination of amino acids, CO_2 formation and ketone formation, leaving no residuum for conversion of fats into glucose. Ketones are utilized efficiently by the diabetic organism (evidence given in detail) without insulin and without the necessity of simultaneous carbohydrate oxidation. Re-examination of the data from calorimetric studies on diabetics with ketosis does not confirm the view that ketosis occurs when the ketone-antiketone ratio of 2:1 is exceeded. Ketosis appears when the tissue metabolism is shifted so far to fat that the body's capacity to handle fat derivatives (2.5 gm./kg./day) is overborne by the ketone-producing mechanism.—*A.T.K.*

THADDEA, S., AND H. HAMPE.

Gonadal hormones and diabetes in the aged. *Zeitschr. f. Altersforsch.* 2: 206. 1940.

In aged persons both impaired activity of the pancreas and gonadal insufficiency play important roles. In normal subjects following injection of 50,000 U. Progynon oleosum or of Testoviron (25 mg. respectively), the fasting blood sugar and the sugar level after injection of 10 U. of insulin are unchanged. The same is true of patients with juvenile diabetes. The same procedure in aged persons results in fall in blood sugar level, and the influence of insulin is enhanced. Oral Progynon, 2×1000 U. daily, or Testoviron for a longer period by subcutaneous injection (10 mg. every other day) lowers blood sugar level, and carbohydrate tolerance is improved. In cases of gonadal insufficiency the urinary creatine is commonly increased, due to splitting of muscle glycogen. In elderly diabetics the high creatine output can be eliminated by sex hormone injection, which acts via the pituitary. Sex hormones apparently have a depressant effect upon the pituitary body in the aged.—*Leo Hess.*

WATERS, E. T., AND C. H. BEST.

The pancreas as an organ of internal secretion. *J.A.M.A.* 117: 852. 1941.

In this review of the association of the pancreas and its internal secretion with diabetes mellitus, insulin is discussed as follows: chemistry, standard, source, insulin content of pancreas under different conditions, secretion, administration, mode of administration, allergy, mode of action, resistance and sensitivity, and possible substitutes. The question of a second internal secretion of pancreas, such as lipocaic, is also discussed.—*C.P.*

WHITE, G., AND E. A. HASSARD.

Retinopathy in diabetes. *Canad. M. A. J.* 44: 586. 1941.

The incidence of diabetic retinopathy increases with advancing age and is frequently but not invariably associated with cardiovascular-renal disease.—*H. Selye.*

PARATHYROID

ALBRIGHT, F.

The parathyroids—physiology and therapeutics. *J.A.M.A.* 117: 527. 1941.

In this glandular physiology and therapy review article the parathyroids are discussed from the standpoint of normal and pathological physiology, hypoparathyroidism, and primary and secondary hyperparathyroidism.—*C.P.*

KAPLAN, D.

Treatment of postoperative parathyroid tetany with ovarian hormones. *Am. J. Surg.* 55: 131. 1942.

On the basis of a postulated relation between ovarian activity and Ca balance, and in view of the chemical simi-

larity between sex hormones and vitamin D, 2 patients were treated with estrogens, progesterone, or both. Alleviation of tetany symptoms was found, although no influence on serum Ca was noted. Relief was attributed to the effects on neuromuscular excitability.—*H.O.H.*

McLean, F. C.

Activated sterols in the treatment of parathyroid insufficiency. *J.A.M.A.* 117: 609. 1941.

In this review article the activated sterols are discussed under the following headings: effectiveness, chemistry, dosage, toxicity, mode of action, dihydrotachysterol, and vitamin D. As comment, the author concludes that vitamin D preparations are as potent and as free from danger as dihydrotachysterol.—*C.P.*

Neller, J. L.

Osteitis fibrosa cystica (Albright). *Am. J. Dis. Child.* 61: 590. 1941.

The case of the syndrome described by Albright is reported in a 7-year-old boy with a history of marasmus in infancy, pigmented spots and frequent fractures. Roentgen evidence of fibrocystic disease was suported by results of biopsy. The blood and urine were normal on both chemical and microscopical analysis except for increase in blood phosphatase. A review of the literature on the subject is given. The author considers that multipld embryonic defects of multiple systems rather than a single one are the most likely causative factors.—*M.B.G.*

Power, F. H., S. Pedersen and W. G. Maddock.

Tetany following sodium chloride replacement therapy. *J. Pediat.* 18: 776. 1941.

Unusual findings in a 15-year-old boy are reported. Symptoms of tetany were absent in spite of a marked degree of alkalosis as indicated by plasma chlorides of 182 mg.%, and CO_2 combining power of 99 vol.%, and intestinal obstruction. Following operation salt in the form of Ringer's solution was given to correct the deficit. Tetany developed on the tenth-post operative day after the return to normal of the plasma chloride, CO_2 combining power and serum Ca.—*M.B.G.*

Strock, M. S.

The mouth in hyperparathyroidism. *New England J. Med.* 224: 1019. 1941

The frequency with which oral symptoms appear in hyperparathyroidism suggests that manifestations about the teeth and within the jaws are of value in recognition of the disease. The dental symptoms are visible or palpable tumors of the jaw, malocclusion or distortion of the normal arrangement of the teeth, cyst-like cavities of the jaws, diminished dental caries, osteoporosis, closely meshed trabeculae and absence of the lamina dura. The fact that, even in extreme cases of demineralization in hyperparathyroidism, caries does not increase is convincing evidence that the resorption of C and P from mature teeth is impossible by way of the blood stream. Disorders of the parathyroid gland should be further studied to throw light on the etiology of dental diseases.—(*Clin. Abstracts*).

THYMUS

Morgan, E. A.

The present status of the thymus gland in pediatric practice. *Canad. M. A. J.* 44: 41. 1941.

A brief review of the physiology and the clinical pathology of the thymus.—*H. Selye.*

THYROID

Abelson, S. M., A. G. Brodie, I. P. Bronstein and S. L. Schreiber.

Muscular macroglossia. Five year observation with cephalometric and speech studies in a case of spontaneous resolution. *Am. J. Dis. Child.* 62: 624. 1941.

In 1937 the authors reported a case of muscular macroglossia and stressed the non-thyroid etiological basis for some types. They noted that idiopathic muscular macroglossia occurred in infants and small children, often in association with congenital anomalies of the genito-urinary and gastro-intestinal tracts. Observation for 5 years on this patient revealed a definite spontaneous reduction in size, without any thyroid therapy.—*M.B.G.*

Aird, R. B.

Experimental exophthalmos and associated myopathy induced by the thyrotropic hormone. *Ann. Int. Med.* 15: 564. 1941.

Exophthalmos induced in the guinea pig by pituitary extracts is re-examined. Evidence is presented that the active fraction is thyrotropic and that hypertrophy and degeneration of the extraocular muscles accounts for the proptosis as in the malignant exophthalmos in man.—*A.T.K.*

Bisgard, J. D.

The relation of hyperthyroidism to hypertension. *Ann. Surg.* 115: 42. 1942.

Essential hypertension was found to exist in 8 per cent of 357 cases of hyperthyroidism (systolic pressure above 170). Elevation of systolic pressure above the physiological level (150) was reported in 25 per cent of the cases. Two types of hypertension emerge in the blood pressure changes following relief of hyperthyroidism, (1) cases with established hypertension, wherein little change in systolic pressure follows, and (2) cases with so-called latent hypertension, in which the blood pressure falls to approximately normal levels. Arteriolar disease probably exists in both types, differing only in degree, being more advanced in type (1).—*H.O.H.*